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Revascularization of the Heart

A Study of Mortality and Infarcts following Multiple Coronary Artery Ligation

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This report on revascularization of the heart is based on work done in this laboratory in the period from Sept. 1, 1949 to Sept. 1, 1951. A brief description of the operation is given. After the operation was done an attempt was made to shift the inflow from the coronary arteries to the graft from the aorta. An attempt was made to occlude all coronary arteries. Four hundred operations were done on 100 dogs. Data on mortality and infarcts are given in this paper.

PREVIOUS reports from this laboratory indicated that blood from the aorta delivered into the coronary sinus protected the heart against ligation of a major coronary artery.[1-4] This protection consisted of reduction in mortality and reduction in size of infarct after a major coronary artery was ligated. The test artery in these experiments was the descending ramus of the left coronary artery occluded in one step at the origin of the artery. During the past two years we extended the arterial ligations to include the other coronary arteries. Attempts were made to ligate the entire coronary artery system in dogs. Records were kept concerning mortality and infarcts as this study progressed and these results are included in this report.

THE OPERATION

The operation as finally developed in this laboratory was done in two stages. The first stage consisted in placing a free graft of jugular vein between aorta and coronary sinus. Special clamps were developed for this operation. The anastomosis between sinus and graft had a stoma which was approximately 8 mm. in length. The stoma on the aortic end was 5 to 6 mm. in length. There were many factors in the technic of the operation which contributed to success or failure. After the graft had been placed blood flowed freely from the aorta, through graft and into the venous system of the heart. Most of the blood escaped into the auricle. The pressure in the coronary sinus after the graft had been placed measured 18 to 22 mm. of mercury. This elevation in pressure was not enough to rupture veins and capillaries in the heart but was sufficient to bring about thickening of the walls of veins so that they could tolerate routinely the higher pressure to which they were exposed at the second stage of the operation. It was readily possible to rupture veins and capillaries by the application of full aortic pressure to these structures. This complication could be obviated by allowing blood to escape freely into the auricle. This fistula also accomplished two additional results that were favorable. The rapid current of blood reduced the rate of thrombosis in the graft. It also prevented excessive thickening and fibrosis of intima which could go on to complete obliteration of veins.[4] Whether the thickening of veins was due to pressure or to alterations in the oxygen and carbon dioxide content of the contained blood was not determined. In order to maintain patency of graft and patency of the sinus and its tributary veins the flow through these channels had to be active and not sluggish. Complete ligation of the sinus at its ostium in the auricle produced a stagnant flow in the graft.[4] One would expect this in dogs because on the other side of the capillary bed was normal coronary artery inflow pressure which was a barrier to any opposing flow. It was observed that, after ligation of one or

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more of the coronary arteries in dogs, the veins became pink indicating retrograde flow.*

The second stage of the operation was done three weeks after the first stage. It consisted of placing a ligature around the sinus near its ostium in the right auricle. This ligature was tied down on a stilet to a diameter of 2.5 mm. or 3 mm. Complete ligation of the sinus was to be avoided. The pressure in the coronary sinus after partial occlusion measured 50 to 70 mm. of mercury. These pressures were readily tolerated as they were reflected back toward smaller veins and capillaries. In the human heart with occlusive disease of the coronary arteries, the veins and myocardium became pink after the second stage of the operation was done and heart was regarded as a protected heart. After the two stages of this operation were done in dogs, the heart was able to withstand coronary artery occlusion.

All operations were done under a closed system of ether anesthesia. A mechanical respiratory (Rand-Wolfe) was used.

Mortality of Operation in Dogs

The two stages of this operation were done in 109 consecutive dogs with no mortality. Several factors made this record possible. One factor in the record was that an attempt was made to care for these dogs in a proper manner.[6] The other factors were the technical surgery, the anesthesia, oxygenation of the blood, and postoperative care. Some of the dogs were subjected to six operations on the heart. These repeated operations produced adhesions and scar tissue which made the technical surgery difficult and dangerous. Repeated dissections of coronary arteries produced a constant threat of hemorrhage, ventricular fibrillation and cardiac asystole. Four hundred operations were done on 100 dogs. Out of these 100 dogs, 30 were lost from immediate complications such as hemorrhage, fibrillation and asystole which occurred during the dissection of the artery. There were 15 postoperative deaths due to pneumothorax, infection, pneumonia, diarrhea from parasites, cerebral complications, and other causes. Thrombosis of the graft occurred in eight dogs. Out of 100 dogs, there were 47 in the series for this study on multiple occlusion of arteries.

Patency of the Graft

The patency rate of the graft in this series of 100 dogs was 92 per cent. Compared with our results in the past, this was the highest rate that we have had. Any deviation in technic influenced this rate. Recently we used a new sinus clamp and the patency rate was 10 out of 15 dogs. The most important factor determining patency was the rapidity of flow in the graft. A rapid flow favored patency; a sluggish flow favored thrombosis. An open fistula into the auricle favored patency. This was one reason for the two-stage operation. The surgical technic also influenced the rate of patency and these factors are not discussed. The patency rate in human patients so far has not been as high as in the experiments.

Method of Producing Occlusion of Coronary Arteries

The method for producing occlusion of a coronary artery consisted of dissection of the artery so that it could be identified and ligated. Partial occlusion of the artery was done by tying a ligature around both the artery and a probe or stilet and then removing the probe or stilet after the knot was tied. One mistake was made in identification of the artery. The degree of occlusion of the artery was always checked by examination of the specimen so that when an artery was said to be occluded it was checked by the specimen. Another consideration in placing these ligatures was that no branch of the artery was missed. Most of the statistics upon coronary artery ligation are based upon experiments in which the ligature might be 1.0 cm. below the origin of the artery; in such experiments one or two branches were usually missed and this made a definite difference in mortality and infarct. The repeated dissections of the coronary arteries were extremely difficult and dangerous because they were imbedded in scar. Another consideration concerning our experiments was that we counted delayed deaths occurring days or weeks after ligation of the

* In human patients in whom this operation was done for coronary artery disease the retrograde flow through veins was considerably more active than it was in dogs with normal coronary arteries.[5] After the graft was placed in these patients, occlusion of the sinus ostium produced marked and extensive pinking of veins and myocardium. Pulsation was noted in the veins. Such active retrograde flow favored success of the operation in patients with occlusive disease in the coronary arteries compared with conditions in the dog.

artery. Our experiments were done under aseptic surgical conditions so that survival was possible.

Another consideration of our method of producing occlusion concerned the time factor of the occlusion. Our ligations, whether complete or partial, were done in abrupt steps. In human patients the occlusion produced by coronary artery disease is frequently gradual, extending over a period of days, weeks, or months. It is known that if the occlusive process is slow enough in patients, the entire coronary inflow may be occluded. The time factor in producing occlusion is an important factor in mortality. This time factor in the occlusive process is important because when the arterial inflow is reduced, another factor appears for consideration. This other factor can be referred to as the factor of safety or the margin of safety. If the heart is to tolerate the occlusive process, the margin of safety over and above minimal requirements for maintenance of the heart beat must be great enough to withstand the inflow reduction. This margin of safety is elastic. It can increase with time so that an inadequate margin of safety producing mortality can be changed to an adequate margin of safety producing recovery if the circulation is given opportunity to make adjustment to the arterial occlusion.

Mortality following Repeated Occlusions

Interval of One Week between Successive Occlusions of Coronary Arteries

The variety of occlusions makes the presentation somewhat complicated. The results are given in table 1. Eleven dogs (group A) were taken in which the graft was instituted in two stages. There was a period of three weeks between the two stages. At the second stage of the operation, immediately after the sinus was partially ligated, the right coronary artery was dissected out and was completely ligated at its origin from the aorta. Four of these dogs died and seven lived. One week after the right coronary artery was ligated, the descending ramus and the circumflex ramus of the left coronary artery were partially occluded in three of these dogs. Two died and one lived. One week later this one survival was operated upon and the descending ramus of the left coronary artery was completely occluded. This dog died.

Three dogs (group B) were taken in which the two-stage operation was done with an interval of three weeks between placing the graft and partial occlusion of the sinus. One week after the second stage was done, the descending ramus and the circumflex ramus of the left coronary artery were partially occluded. One animal died, two lived. One week later these two survivals were operated upon and the descending ramus was completely occluded. Two dogs survived. One week later these two dogs had the circumflex artery completely occluded. One died, one lived. One week later the one survival had the right coronary artery completely occluded. This dog lived for 35 minutes. *The specimen showed all coronary arteries including the septal artery to have been completely occluded.*

Another dog (group C) had both stages of the operation done three weeks apart. One week after the second stage was done, the circumflex ramus of the left coronary artery was completely occluded. The dog lived. One week later the right coronary artery was completely occluded. The dog died.

Seven dogs (group D) had both stages of the operation done three weeks apart. One week after the second stage was done, the left common coronary artery above the septal branch was partially occluded to a diameter of 2.5 mm. One dog died and six lived. One week later these six dogs were operated upon and the common left coronary artery was partially occluded to a lumen of 1.5 mm. Four dogs died and two lived. One week later these two survivals had complete occlusion of the common left coronary artery and both died.

Comment on These Experiments. Under the conditions of the experiment it would appear that the graft did not protect seven dogs from complete occlusion of the right coronary artery. One dog survived complete occlusion of all coronary arteries for a period of 35 minutes. It was our opinion that the blood supply from the aorta through the graft made this possible. Total occlusion of the common left coronary artery was not accomplished even though this artery was taken down in stages. It was our

opinion that an interval of one week between successive occlusions of the coronary arteries was not long enough to give the best results. We believed that the circulation needed a longer period of time to make adjustments to the inflow occlusions. We are of the opinion that the margin of safety following occlusion can increase with time up to a certain point, so that survival might follow the next occlusion if an adequate interval of time existed between the occlusions.

Interval of Three Weeks between Successive Occlusions of Coronary Arteries

In table 2 the results are shown. An attempt was made to produce complete occlusion of the left common coronary artery above the septal branch in seven dogs (group A). The graft had been placed in two stages as usual before the artery was occluded. Three weeks after the second stage was done, the left common coronary artery was partially occluded to a diameter of 2.5 mm. Two dogs died and five survived. Three weeks later, the right coronary artery was completely ligated in these five dogs. Three died and two survived. Three weeks later, the left common coronary artery was partially occluded to a diameter of 1 mm. in the two surviving animals. Both dogs died.

These experiments indicated the high mortality in experimental occlusion of the left common coronary artery even in the presence of the graft and even when the occlusions were done in stages. It was decided to occlude the two major branches of the left coronary artery instead of the common left artery itself.

The graft was placed in 15 dogs (group B) and the second stage was done three weeks after the first stage. Three weeks after the second stage was done the descending ramus of the left coronary artery was totally occluded at its origin. One animal died and 14 lived. Three weeks later the right coronary artery was completely occluded at its origin in one stage in six of these dogs. One died and five lived. Three weeks later the circumflex ramus of the left coronary artery was completely occluded in one stage in these five dogs. Three died and two lived. In one of these dogs the death occurred immediately after the artery was ligated. In the other two dogs death occurred seven days and 22 days after ligation of the artery. The significance of the delayed deaths was that these dogs almost survived the ligations. Indeed it would be correct to state that at the end of the six days following the last occlusion there were four living dogs with complete occlusion of all three major coronary arteries. The two long term dogs were killed after five months. These dogs were believed to have had total coronary occlusion. The specimens from these dogs showed complete occlusion of all arteries except the septal branch. The check by autopsy examination of the specimen was essential because while these dogs were alive we believed that the septal branch was also occluded.

By altering the procedure another animal was obtained in which we believed total occlusion was accomplished. The remaining eight out of 14 dogs that survived ligation of the descending ramus of the left coronary artery were operated upon after an interval of three weeks and the circumflex ramus of the left coronary artery was ligated in one stage at its origin. Six died and two lived. Notation is made here that, if we had interposed ligation of the right coronary artery between ligations of the two major branches of the left coronary artery, the survival record might have been greater than two out of eight. The adjustment to the occlusions might have been better. Of the two survivals, one was operated upon three weeks later and the right coronary artery was totally occluded at its origin in one step. This dog survived. It was kept for a period of five months. It was then killed, and the specimen showed complete ligation of the three major coronary arteries. The septal branch was patent.

Two dogs (group C) were subjected to total ligation of the right coronary artery three weeks after the second stage of the graft. Both dogs lived. Three weeks later one of these dogs had total ligation of the descending ramus of the left coronary artery. This dog lived. Three weeks later the dog had the circumflex ramus of the left coronary completely ligated and died.

One dog (group D) was subjected to total ligation of the circumflex artery three weeks

after he second stage of the graft and lived. Three weeks later the right coronary artery was tally ligated and the dog survived.

Comment on These Experiments. The septal artery originates from the common left coronary artery or from the descending ramus of this artery. In many instances the septal branch was ligated together with the descending ramus of the left coronary artery. We could not be certain whether the septal branch was ligated with the descending ramus until the specimen was examined. In this series there were five dogs that survived complete ligation of the descending ramus of the left coronary artery, the circumflex ramus of the left coronary artery and the right coronary artery. Only the septal branch was patent. One of these dogs died seven days and one died 22 days after ligation of the circumflex ramus of the left coronary artery. The remaining three dogs were kept for five months. During this period of time the dogs were active and appeared to be normal. Electrocardiograms on these dogs, taken at rest, showed minimal evidence of infarction. These dogs were given an anesthetic; the chest was opened and the graft was identified. The graft was clamped off for a period of 30 minutes. There was no change in the electrocardiogram and there was no objective change in the heart beat while the graft was occluded. The only interpretation that can be given to these observations is that the graft was not essential to the maintenance of the heart beat for a period of 30 minutes under the conditions of the experiment. This raised doubt as to whether a significant quantity of blood flowed in a retrograde direction in these experiments. We have evidence to show that retrograde flow occurs immediately after arterial occlusion. Studies on retrograde flow occurring days or weeks after arterial occlusion are being carried out. The dogs were killed and the specimens were examined. In the hearts of two of these dogs complete occlusion existed in the descending ramus of the left coronary artery, the circumflex ramus of the left coronary artery and the right coronary artery. Only the septal branch was patent. This arose from the common left at a level proximal to the descending ramus. In the third specimen all coronary arteries, including the septal branch, were completely ligated except that the occlusion of the circumflex ramus was not quite complete. It had a lumen of 1.0 mm. and it is possible that this artery was completely occluded at the time the ligation was placed and that this small lumen developed subsequently.

Survival and mortality following complete occlusion in one stage of one, two and finally three major coronary arteries can be obtained from tables 1 and 2. Table 3 summarizes these results. Out of the 47 ligations there were 29 that survived one-stage ligation of one major artery: right coronary seven in group A table 1, two in group A table 2 and two in group C table 2; descending ramus two in group B table 1 and 14 in group B table 2; circumflex ramus one in group C table 1 and one in group D table 2. Out of these 29 survivals there were 10 that survived complete occlusion of a second major artery: one in group B table 1, seven in group B table 2, one in group C table 2 and one in group D table 2. Out of these 10 survivals there were three that survived occlusion of the third major artery: three in group B table 2. In addition to these three long term survivals there was one dog that lived seven days and one that lived 22 days after all three major arteries were occluded (two in group B table 2). Table 4 shows the figures for each of the three arteries: descending ramus, 17 (15 in group B table 2 and two additional dogs not in the table); right coronary artery, 13 (group A table 1 and group C table 2); circumflex ramus, two (group C table 1 and group D table 2). Partial occlusion of the left common coronary artery was done in 14 dogs (group D table 1, and group A table 2). A combination of partial occlusion of the descending ramus and partial occlusion of the circumflex was done in three dogs (group B table 1).

Discussion

Several conclusions can be drawn from these experiments. The survival rate in the animals referred to in table 2 was greater than in those referred to in table 1. It would appear that an interval of three weeks between operations on

the coronary arteries (table 2) gave a higher survival rate than occurred when this interval was one week (table 1). Perhaps the dog required a longer period than one week to recover from one operation before the next operation was done. This would involve such general considerations as nutritional disturbance and other side effects of the anesthetic and the operation. Another factor concerned the adjustments of the circulations that take place after a coronary artery was partially or completely occluded. These adjustments were important and required time to run their course and reach an end point. We have had experience in the past which has led us to attach importance to this factor.

TABLE 1.—*Both Stages of Operation. Serial Ligation of Arteries. Interval between Ligations One Week*

Coronary Artery Ligated	Number of Dogs	Died	Survived
Group A			
Right	11	4	7
Descending ramus, partial. Circumflex ramus, partial.	3	2	1
Descending ramus, complete.	1	1	
Group B			
Descending ramus, partial. Circumflex ramus, partial.	3	1	2
Descending ramus, complete	2		2
Circumflex ramus, complete	2	1	1
Right	1	1	
Group C			
Circumflex ramus, complete	1		1
Right	1	1	
Group D			
Left common, partial, 2.5 mm.	7	1	6
Left common, partial, 1.5 mm.	6	4	2
Left common, complete	2	2	

The mortality following ligation of the right coronary artery in group A of table 1 was higher than occurred in normal control dogs. A satisfactory explanation of this cannot be given. In other experiments not included in this series the mortality was lower when an interval of three weeks or longer existed between partial occlusion of the sinus and subsequent ligation of this artery. We believe that the time interval was a factor in this mortality.

TABLE 2.—*Both Stages of Operation. Serial Ligation of Arteries. Interval between Ligations Three Weeks*

Coronary Artery Ligated	Number of Dogs	Died	Survived
Group A			
Left common, partial, 2.5 mm.	7	2	5
Right	5	3	2
Left common, partial	2	2	
Group B			
Descending ramus	15	1	14
Right	6	1	5
Circumflex	5	3	2
Circumflex	8	6	2
Right	1		1
Group C			
Right	2		2
Descending ramus	1		1
Circumflex	1	1	
Group D			
Circumflex	1		1
Right	1		1

Complete occlusion of the common left coronary artery above the septal branch carried out in stages was not successful, as shown in group D of table 1 and group A in table 2. This artery could be occluded to a lumen of 1.0 or 1.5 mm. It would appear that the amount of blood going through such a small opening was necessary for the heart beat. The two major branches of the left coronary artery excluding the small septal artery were completely occluded. It would appear that the septal branch might have been a factor in mortality and yet

in the ligation of the descending ramus the septal branch was frequently included with the descending ramus and recovery occurred.

The highest recovery rate in arterial occlusions occurred in the dogs composing group B of table 2. We believed that the order of occlusions was a factor in this recovery rate. This order was first the descending ramus, second the right coronary artery and third the circumflex ramus. It would appear that this rotation was followed by the most favorable circulatory adjustments after each occlusion.

The recovery rate following complete occlusion of the descending ramus in one stage (16 out of 17 dogs) was of special significance (table 4). The two-stage operation with the institution of the graft made this possible. The operation protected the heart after this artery was occluded. After this series of experiments was done this artery was ligated in 13 additional dogs. Out of these there were seven deaths and six recoveries. These experiments were done during a period of hot weather. The interval between the second stage of the operation and the arterial ligation was two weeks. One dog died when the artery was being dissected and before the artery was occluded. Perhaps factors other than the ligation of the descending ramus determined this mortality.

Beck, Stanton, Batiuchok and Leiter[1] reported on mortality and recovery following ligation of this same test artery. In these dogs an anastomosis was made between the carotid artery and the coronary sinus and the sinus at its ostium in the auricle was either partially or completely occluded. Out of 10 dogs with patent anastomosis there were eight recoveries and two deaths. In the two dogs that died, deaths were delayed. These dogs almost survived. In 10 identical experiments in which the graft was occluded by thrombosis the mortality was seven and the recovery was three.

A second series of experiments was reported by McAllister, Leighninger and Beck.[4] The test artery was ligated in 13 dogs with 12 survivals and one death. At the time this report was made several dogs were kept for long term study. Since the report was made and since the specimens were examined it was found that the test artery was ligated in 10 dogs with one death. The descending ramus was missed in three specimens.

The total experience for ligation of this test artery from this laboratory was 37 dogs with 33 recoveries and four deaths. If a recent series not in these tables was included, the total figure was 50 dogs with 39 recoveries and 11 deaths. This was a mortality of approximately 9 per cent with the lower figure and 22 per cent with the higher figure. Our experience with ligation of this test artery in over 100 normal control dogs was a recovery rate of 30 per cent and a mortality rate of 70 per cent. It was obvious that the two-stage operation gave definite protection to the heart after occlusion of the test artery.

TABLE 3.—*Survival after Successive One-Stage Ligations of Three Major Coronary Arteries—Descending, Circumflex, Right.*

Number of Ligations	One Artery	Two Arteries	Three Arteries
Total Number of Dogs	47	29	10
Survivals	29	10	3

TABLE 4.—*Complete Occlusion of Coronary Arteries in One Stage*

Artery	Total Dogs	Survival	Dead
Descending Ramus	17	16	1
Right	13	9	4
Circumflex Ramus	2	2	0

We do not have statistical evidence to indicate that the operation made it possible to ligate all three of the major coronary arteries except the septal branch with recovery. Ligation of the circumflex ramus alone in normal dogs had a high mortality. Our estimation of this mortality in normal dogs was about 90 per cent. Allen and Laadt reported mortality of 82 per cent within 24 hours after ligation of the circumflex artery at its origin.[7] We never attempted ligation of both descending ramus and circumflex ramus in normal dogs but we would estimate the mortality to be 100 per cent.

INFARCTS

The infarcts that developed after ligation of one or more coronary arteries were classified as

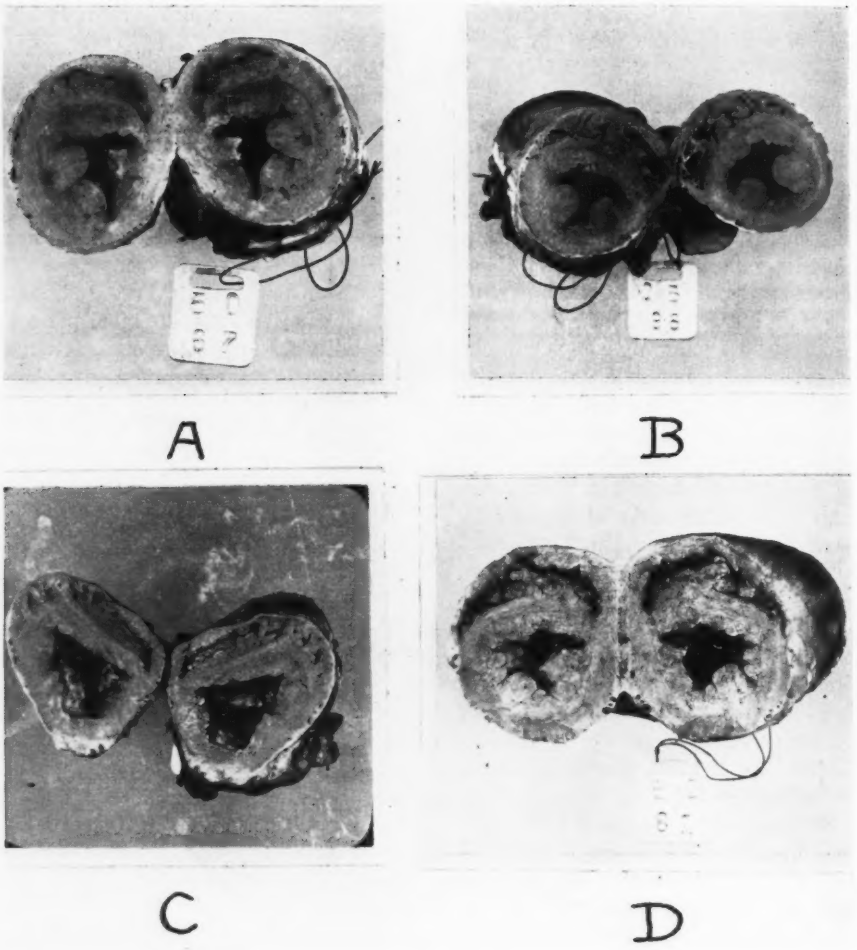

FIG. 1. Photographs of hearts five months after the last coronary artery was occluded. *A*. Complete occlusion of descending ramus, circumflex ramus and right coronary artery. Only the septal branch was patent. There was slight fibrosis of myocardium but there was no extensive destruction and no thinning of the myocardium. *B*. Complete occlusion of circumflex ramus and right coronary artery. The descending ramus and the septal branch were patent. Small areas of fibrosis were present, but no extensive infarct. *C*. Complete occlusion of descending ramus, septal branch, and right coronary artery. The circumflex ramus was occluded to a lumen of 1 mm. With the exception of this small lumen all coronary artery inflow was occluded. A few small areas of fibrosis were present beneath the endocardium. There was no extensive infarct. *D*. Complete occlusion of descending ramus, circumflex ramus and right coronary artery. Only the septal branch was patent. There was no extensive destruction of heart muscle. The specimen was discolored by injection of colored material into the coronary arteries.

large, small and absent. A large infarct measured approximately 4 cm. in its greatest transverse diameter. A small infarct was less extensive but showed a definite area of scar. The term no infarct was applied to those specimens in which the fibrosis was limited to discrete areas of about 1.0 to 2.0 mm. in diameter. This definition of no infarct was not strictly accurate

and was used to indicate little or no destruction of heart muscle.

Of 29 specimens in which one artery was ligated the infarct was large in four, small in three and "absent" in 22. Of 10 specimens in which two arteries were ligated the infarct was large in two, small in one and "absent" in seven. Of three specimens in which three major coronary arteries were ligated (all coronary arteries except the septal branch) the infarct was large in none, small in one and "absent" in two.

Of 16 specimens in which the descending ramus of the left coronary artery was ligated, the infarct was large in two, small in two and "absent" in 12. Of nine specimens in which the right coronary artery was ligated the infarct was large in one, small in one and "absent" in seven. Of two specimens in which the circumflex ramus was ligated the infarct was large in one, and "absent" in one. Four specimens are shown in which several coronary arteries were occluded (fig. 1). None of these specimens showed extensive destruction of the heart muscle.

Discussion

We have data from this laboratory on infarcts following ligation of the descending ramus of the left coronary artery in normal control dogs.[8] In a series of 50 dogs in which this artery was totally occluded at its origin in one stage there were 15 dogs that survived this operation. The infarct was classified as large in seven, intermediate in size in four and small in four. In no specimen was there no infarct. The conclusion was made that this two-stage operation protected the heart against destruction of myocardium after the descending ramus of the left coronary artery was occluded. In some of these protected hearts there was little or no destruction of heart mucle following occlusion of this artery. In our experience this never occurred in normal control dogs. No doubt the two-stage operation afforded similar protection to the myocardium following occlusion of the circumflex ramus of the left coronary artery but our data for this artery are inadequate to make this statement. The recovery rate following ligation of the circumflex ramus in normal dogs was such that a satisfactory series for the normal was never obtained.

Conclusions

1. A free vein graft was placed between aorta and coronary sinus. Several weeks later the coronary sinus was partially occluded at its ostium in the right auricle. Statistics on mortality from these operations and patency of graft were given.

2. After this operation was done in two stages it was possible to produce almost total occlusion of all coronary arteries. Total occlusion of all coronary arteries with long term recovery was not accomplished but complete occlusion of the descending ramus, the circumflex ramus and the right coronary artery with long term recovery was accomplished.

3. The operation did not give complete protection against experimental occlusion of major coronary arteries but it afforded significant protection. This protection was shown in reduction of mortality and in reduction in size of infarcts after occlusion of major coronary arteries.

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Revascularization of the Heart

Histologic Changes after Arterialization of the Coronary Sinus

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A free graft of vein was placed between the aorta and coronary sinus. Three weeks later the sinus was partially occluded at its ostium in the right auricle. Blood from the aorta was made available to the myocardium by way of the venous system. After these procedures were done a histologic study of the venous and arterial channels was carried out. The coronary sinus and its tributaries showed hyperplasia of the intima. The anterior cardiac veins showed dilatation with little or no hyperplasia of intima. None of the veins became occluded. Complete occlusion of major coronary arteries was done. These arteries distal to the occlusion showed medial sclerosis and atrophy. They did not show thrombosis. The myocardium distal to an occluded artery showed many vascular channels.

AN OPERATION was developed in this laboratory which made an additional source of aortic blood available to the myocardium.[1] This operation is described on page 801, in this issue.

It was shown by experiment that this operation protected the heart against occlusion of a major coronary artery. In view of the fact that this operation appeared to have therapeutic possibilities for patients with coronary artery disease, this study on the anatomy of the vascular system was carried out. The specimens used in this study were those upon which Hahn and Beck carried out multiple ligation of major coronary arteries.[3]

Method of Study

This report was based upon a study of 37 specimens. A variety of procedures was carried out on the dogs from which these specimens were obtained. The two stage operation was done with an interval of three weeks between the placing of the graft and the partial occlusion of the sinus at its ostium in the right auricle. One or more major coronary arteries were ligated subsequently. Figure 1 shows the various areas from which sections were made. The sections were stained by hematoxylin and eosin and also by the trichrome and van Gieson-Weigert method. The following protocol illustrates the sequence of events in producing one of the specimens for study. (1) A free vein graft was introduced between aorta and coronary sinus; (2) three weeks later the coronary sinus was occluded at its ostium to a diameter of 3 mm.; (3) coronary arteries were ligated at intervals of three weeks to include (a) complete ligation of descending ramus and septal artery, (b) complete ligation of right coronary artery and (c) partial occlusion of circumflex ramus to a lumen of 1 mm. In this experiment the graft was patent for eight months; the coronary sinus was partially occluded for seven months, the descending ramus and septal arteries were completely occluded for six months, the right coronary artery was completely occluded for five and one-half months and the circumflex ramus was partially occluded for five months. Extensive occlusion of coronary arteries similar to that accomplished in this experiment were obtained in other experiments.

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Results

The Graft

The appearance of the graft was similar in each specimen. The original vein had undergone marked alterations so that it was difficult to identify intima, media and adventitia (fig. 2, *A* and *B*). The graft was a tube of fibrous tissue lined by a smooth endothelium. The media and adventitia were composed of collagenous and coarse elastic fibers. The intima consisted of normal endothelial lining beneath which were elastic fibers and areolar connective tissue. The vasa vasorum of the graft showed marked intimal hyperplasia together with a development of elastic and connective tissue cells.

Grossly the graft was a strong structure capable of withstanding high pressures. It usually dilated about one-fourth of its normal diameter but dilatation did not always occur. In several instances the dilatation of the graft might be described as slightly aneurysmal, but there was no evidence to indicate that dilatation was progressive with time. There was no evidence to indicate that a vein graft was not satisfactory and that an arterial graft should be used instead of a vein graft.

The Coronary Vessels

Arteries. Sections were taken in areas A, B, C, D, S, and CV of figure 1. In general an artery that had been ligated showed atrophy of the various components of the arterial wall distal to the ligature (fig. 3). The adventitia consisted of collagenous tissue and coarse elastic fibers. The elastica externa was usually present but was always broken up by penetrating collagenous fibers. The muscle and elastic fibers of the media were infiltrated by fibrous connective tissue. The internal elastic membrane was well developed. The intima was reduced to a thin endothelial layer of cells. The lumen of these arteries remained patent even though the main artery was totally occluded for a period of six months. Patency was observed throughout the arterial system down to the smallest arterioles. The degree of medial sclerosis of arteries was greatest in the larger arteries and least in the smaller arteries.

Veins. The coronary sinus was dilated in almost all specimens. The sinus is shown in figure 4. The intima was thin and consisted of a layer of endothelium and some connective tissue. The media and adventitia consisted of sclerotic collagenous material and coarse elastic fibers. Muscle fibers could not be recognized in the media. This appearance of the sinus was similar to the appearance of the graft.

The veins draining into the coronary sinus presented a different appearance. Marked hyperplasia of the intima was present in these tributaries (fig. 2*C*). This appeared to be a hyperplasia of connective and elastic tissue elements. In the larger veins a definite medial layer was present and the muscle fibers were dissociated by infiltrating bands of collagenous fibers which appeared to penetrate into the intima. The adventitia contained an abnormal amount of collagenous tissue with elastic fibers.

An artery and vein of approximately equal size are shown in figure 2*D*. In this illustration it was readily possible to recognize the intimal hyperplasia of the vein. The appearance of the vein was much like that of an artery and the appearance of the artery was much like that of a vein.

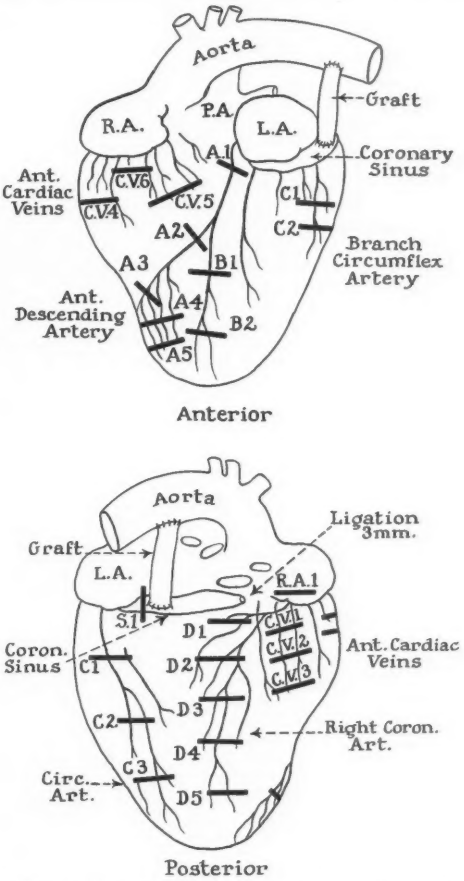

FIG. 1. Diagrams of heart. Anterior and posterior views showing areas from which sections were made.

The anterior cardiac veins drained independently into the right auricle. These veins were not exposed to similar degrees of stasis and pressure. Communications between these two systems of veins may develop, but as a

rule the anterior cardiac veins did not become an important run-off for blood from the graft system. The anterior cardiac veins showed only some dilatation of the normal wall without showing any of the intimal hyperplasia of the coronary sinus system. The intima was a thin layer of endothelium (fig. 2*E*). The external elastic membrane was thin and the adventitia was composed of collagenous fibers.

Sections taken from the interventricular septum showed structures comparable to those found elsewhere. Hyperplasia of intima was present in some of the veins and simple dilatation was found in others.

Thrombosis was not found in any of the veins in this study of 37 specimens. This negative finding applied to all veins; the sinus system and its tributaries and also the anterior cardiac veins and their tributaries.

Myocardium

The specimens showed that it was possible to ligate one or more major coronary arteries with the production of little or no gross evidence of infarction. Under the microscope, however, areas of fibrosis were always found in the myocardium that had been supplied by the artery which was occluded even though the specimen did not show an infarct or areas of fibrosis to the naked eye. In some specimens there was no noticeable atrophy of the ventricular wall and grossly the muscle appeared to be normal.

In those specimens in which a definite infarct was present the infarcted area appeared to show an unusual degree of vascularity (fig. 2*F*). Many vessels were interposed in a mesh of fibrous scar and in such scars there were no muscle fibers regardless of the degree of vascularity. In these scars it was almost impossible to distinguish between arterioles and hyperplastic venules. In our opinion most of these vessels were venules with a marked degree of intimal hyperplasia. In the periphery of an infarct dilated venules engorged with red blood cells were consistently observed.

The arterioles of the myocardium were normal in all sections (fig. 5). The small arteries or arterioles showed none of the medial sclerosis observed in large arteries. The small venules did show changes similar to those shown by the larger veins. If the venules were connected to the coronary sinus system they showed intimal hypertrophy, whereas, if the venules were connected to the anterior cardiac vein system they showed dilatation or normal structure.

Arterialization of the Sinus, Complete Sinus Ligation, without Coronary Artery Occlusion

In specimens from dogs in which this procedure had been carried out, the degree of intimal hyperplasia of the veins was more pronounced than in the specimens already described. The condensation of elastic fibers was more pronounced. Complete thrombosis of many of the veins was found. These observa-

FIG. 2. *A*. Transverse section of wall of graft eight months after placement. Note the condensation of collagenous and coarse circular elastic fibers marking the original adventitial and medial structures. An endothelial membrane resting upon a thin layer of connective tissue elements probably represents the original intima. In addition, note the remarkable intimal hyperplasia of the vasa vasorum. Van Gieson-Weigert stain.

B. Transverse section of graft with greater magnification. Van Gieson-Weigert.

C. Transverse section of tributary sinus vein. There is a striking hyperplasia of the intima consisting predominantly of connective and elastic tissue elements. The media is dissociated by infiltrating bands of collagenous fibers which seemingly penetrate into the basal layer of the intima. Van Gieson-Weigert stain.

D. Transverse section of arteriole and venule of left ventricle. Note the striking difference in thickness of the walls of the vessels. The venule again presents the characteristic intimal hyperplasia. Trichrome stain.

E. Transverse section of anterior cardiac vein and accompanying artery. The artery had been ligated proximally. The vein shows rather marked thinning of all layers. Note the medial sclerosis of the artery. Van Gieson-Weigert stain.

F. Transverse section of myocardium showing an infarct. Note the abundance of small vessels in the sclerotic muscle tissue. 125 ×. Van Gieson-Weigert.

(*The use of color in this illustration is made possible by a grant from Winthrop-Stearns, Inc., to the publication fund of the American Heart Association.*)

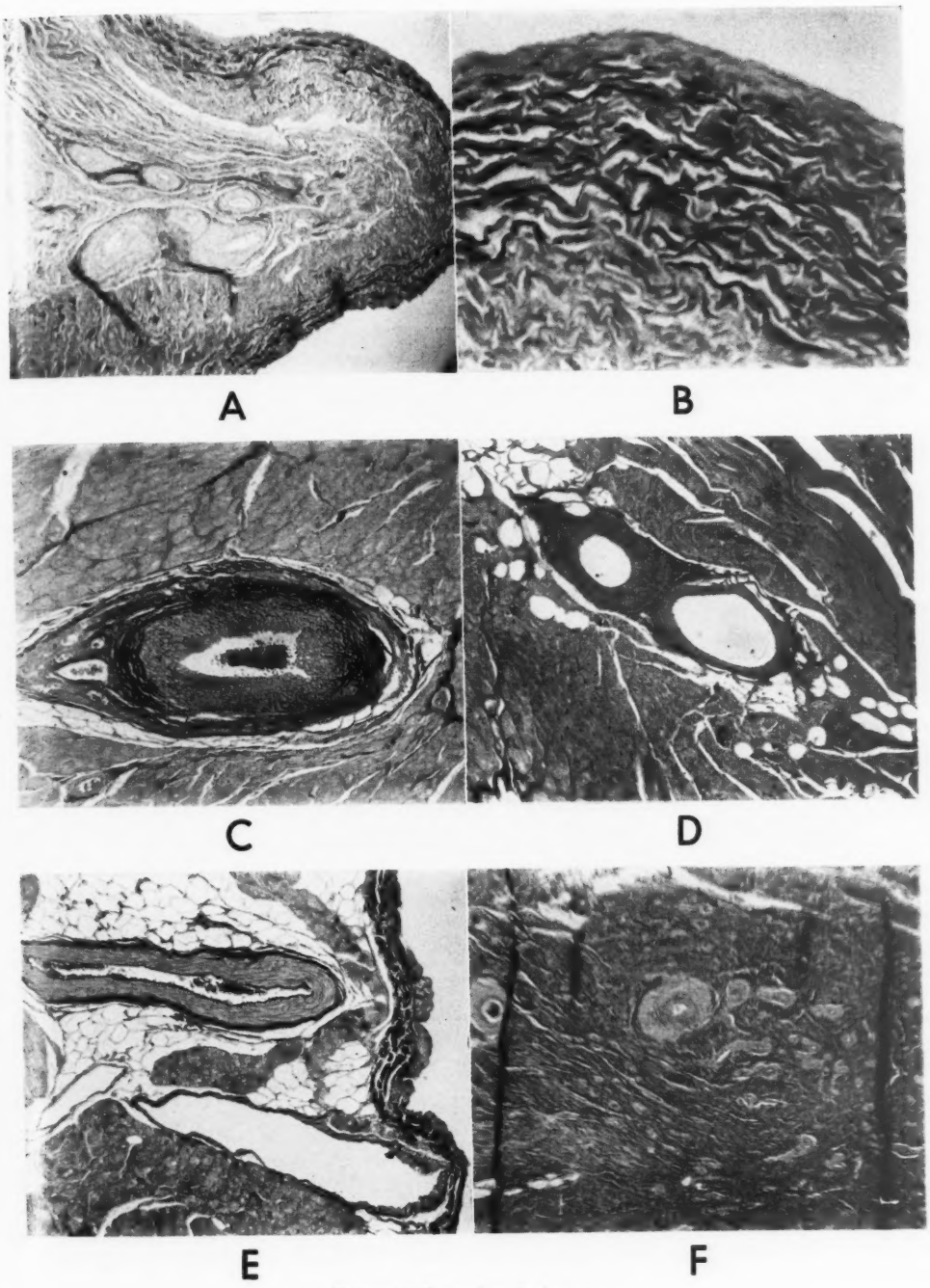

FIGURE 2. Legend on facing page.

tions confirmed those reported by McAllister, Leighninger and Beck.[2] Marked intimal hyperplasia of veins with secondary thrombosis was found in those specimens in which the sinus ostium was completely occluded but in which none of the coronary arteries were occluded. It appeared that circulation could not be maintained in this system. The circulation was "locked," so to speak. Blood could not escape into the auricle by way of a completely occluded sinus ostium and it could not go in a retrograde direction through the myocardium because the coronary arteries were patent and a normal arterial pressure level was maintained on the arterial side of the capillary bed. The anterior cardiac veins did not develop into an adequate run-off. The blood had no place to go and it would appear that movement of blood is necessary for a blood vessel to maintain itself as a vessel. This type of vascular system could not maintain itself as an open functional system. It was given an extensive trial over a period of several years in this laboratory before it was abandoned.

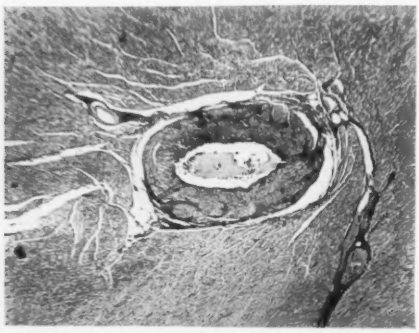

FIG. 3. Transverse section of artery five months after proximal ligation. Rather extensive sclerosis of the medial layer is present. The intima is reduced to an endothelium. Van Gieson-Weigert stain.

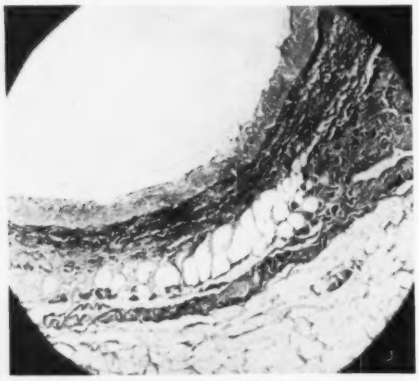

FIG. 4. Transverse section of the coronary sinus eight months after placement of graft. The sinus is dilated. The intima is represented by an endothelium with a small band of connective tissue. There is sclerosis of the subintimal layers. 175 ×. Van Gieson-Weigert stain.

FIG. 5. Transverse section of arteriole and venule of the sinus system. The arteriole is normal in appearance. A small venule just above the arteriole is dilated. The other venule reveals the characteristic intimal hyperplasia. Trichrome stain.

Arterialization of the Coronary Sinus without Occlusion of the Sinus Ostium and without Occlusion of Coronary Arteries.

In this type of experiment blood flowed from aorta, through graft, into sinus and into right auricle. In these specimens in which the coronary arteries were normal there probably was no retrograde flow into myocardium. The mean pressure in that portion of the sinus between the graft and sinus ostium measured 18 to 22 mm. Hg. The venous channels from these specimens showed some slight dilatation but none of them showed intimal hyperplasia.

Specimens Showing Thrombosis of Graft and Sinus. In these experiments there was no flow through the graft and into the sinus. These specimens were similar to normal hearts in which the sinus was completely occluded by a ligature. In those specimens with thrombus

formation the veins proximal to the thrombus were dilated without showing intimal thickening. In some of these specimens the tributaries to the coronary sinus showed thrombus formation. After ligation of the coronary sinus the pressure in the sinus system rose to aortic levels and the pressure remained elevated after the ligation was done.[2]

Discussion

Definite alterations in structure were observed in the coronary sinus and its tributaries after arterial blood was delivered into the sinus and the site of exit of the blood into the auricle was partially occluded. The principal structural alteration was intimal hyperplasia, occurring as early as six weeks after the graft was placed and the sinus was partially occluded. In these experiments the intimal hyperplasia did not produce occlusion of the veins of the coronary sinus system. The anterior cardiac veins were almost always dilated or normal. Rarely was any thickening of intima found in the vessels of this system. In those areas where the two systems came together, veins with intimal hyperplasia and normal veins were observed in the same section. This was found in sections taken from the region of the anterior interventricular sulcus, the interventricular septum and the posterior aspect of the left ventricle.

Definite alterations in structure were also observed in arteries distal to the point of arterial occlusion. This structural alteration consisted primarily of atrophy of the media. The artery distal to the ligature remained patent and patency of a vessel suggested function. The patent artery with proximal occlusion no doubt carried blood. If the artery were severed blood emerged from the cut end.

Comment might be made concerning the cause of the intimal hyperplasia in veins as described in this paper. If the hyperplasia were due to pressure alone, one would expect that hyperplasia would have been found in those specimens in which the sinus had been occluded by a ligature or by thrombosis. Hyperplasia of intima was not found in those specimens. A possible factor in the production of hyperplasia was pulsatile pressure. Could pulsatile pressure as contrasted to a more or less constant static pressure produce these changes? Could alterations in oxygen and carbon dioxide content of the blood in the venous system produce such alterations? An answer to these questions cannot be given.

It was interesting that the vasa vasorum of the vein graft showed intimal hyperplasia whereas the graft itself did not show this alteration in structure.

Several comments can be made concerning the changes in the myocardium supplied by a major coronary artery that had been previously occluded. In the area supplied by the occluded artery there appeared to be an increased number of veins filled with blood. Between these veins were areas of scar which suggested that oxygen exchange requiring the thin walls of capillaries was not adequate to preserve the viability of muscle fibers.

Conclusions

1. Arterialization of the coronary sinus system, with partial ligation of the sinus at its ostium, produced marked alterations in structure of the sinus and its tributaries. This alteration was primarily fibroelastic proliferation of the intima. This alteration in structure was observed after six weeks and it did not proceed to complete occlusion of veins.

2. Major coronary arteries underwent structural alterations after they were occluded by ligature at the origin of the artery. Distally the arterial wall showed atrophy with sclerosis of the media.

3. The anterior cardiac veins showed little or no structural change.

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Dynamic Responses of the Right Ventricle following Extensive Damage by Cauterization

By ABRAHAM KAGAN, M.D.

Previous observations that major destruction of the right ventricular walls causes but slight changes in venous and arterial pressures were confirmed. Furthermore, additional observations indicated that the compensatory reaction of the damaged ventricle to stress is diminished surprisingly little. The results are considered evidence that the cauterization procedure and others of a similar nature do not produce right heart failure and, therefore, would not be expected to cause venous congestion. The subsidiary muscular mechanism which maintains the right ventricular pump remains enigmatic; but evidence is submitted that the damaged right ventricle is regulated independently of the left.

REINVESTIGATIONS of apparently well established functions occasionally reveal that generally accepted concepts require amendment or drastic revision. This has recently been the case following studies on right ventricular function. In 1943, Starr and his associates,[1] who were interested in problems of right heart failure, discovered that almost complete thermal destruction of the right ventricle in dogs eventuated in no appreciable elevation of venous or fall of arterial pressures. The complementary studies of Rodbard and Wagner,[2] who primarily stressed low pulmonary arterial resistance, showed that the driving force of right ventricular contraction is not necessary for maintenance of an adequate blood flow to the left atrium. However, the studies of Bakos[3] clearly indicated that the pulmonary arterial pressures and, by inference, the stroke volumes of the right ventricle are not significantly reduced after almost complete inactivation of the right ventricular walls by cauterization. Two inferences might be allowable:

1. Under resting conditions, extensive destruction of the entire right ventricular walls does not lead to right heart failure, a fact of considerable clinical importance.

2. The force expelling blood into the pulmonary circuit can be derived from sources other than contraction of the external walls of the right ventricle, a fact of great physiologic interest. The corollaries do not necessarily follow that contractions of the right ventricular walls are unimportant normally, or that increased vigor of their contractions does not contribute to augmented stroke volumes.

The great importance of the problems presented warranted further experimental studies, first of all, to substantiate the conclusion of previous workers that the right ventricle can maintain essentially normal propulsive force after nearly complete destruction of the external walls, second, to elucidate the subsidiary mechanisms by which essentially normal stroke volumes are possible and, finally, to test how the reaction of such a damaged right ventricle to stress differs from that of a normal one. The present investigation concerned itself with these problems.

METHODS

Mongrel dogs weighing between 10 and 20 Kg. were anesthetized with morphine sulfate, 5 mg. per kilogram subcutaneously, and sodium barbital, about 200 mg. per kilogram intravenously. The chest was opened by a midsternal incision, and mild pulmonary ventilation was maintained by an inter-

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This investigation was carried out during the tenure of a Postdoctorate Research Fellowship of the U.S. Public Health Service as partial fulfillment of work in a Training Course for Cardiovascular Investigators (1950-51). The expenses for this investigation were defrayed by a grant from the American Heart Association, Inc., to Dr. C. J. Wiggers, Program Director.

mitter[t] positive pressure respirator. The pericardium [was] slit longitudinally and the heart was supporte[d] in a pericardial cradle without impeding right atrial [f]illing.

Ao[r]tic blood pressure was recorded optically by mean[s] of a rigid cannula inserted via the left common [c]arotid artery until its tip just reached the arch [o]f the aorta. The cannula was connected throu[g]h a short length of lead tubing to a modified Gregg manometer. Mean femoral venous pressure was [m]easured by periodic reading of a saline manome[t]er connected to a femoral vein. Phasic change[s] in right atrial and right ventricular pressures [w]ere recorded optically by rigid cannulas connected by short lengths of lead tubing to Gregg manometers of appropriate frequency and sensitivity. All measurements were made using the level of entrance of the superior vena cava into the right atrium as the zero reference level. In a few experiments movements of the right ventricular wall were recorded optically by a Frank segment capsule connected to a myocardiograph which was sutured to the right ventricular wall. (For technic see Tennant and Wiggers.[4])

In all experiments the entire free right ventricular wall was damaged as extensively as seemed consistent with its continued integrity by repeated applications of the tip of a Geiger electrocautery unit. The desired degree of damage was achieved in approximately one hour. Arrhythmia could generally be avoided by increasing the temperature of the cautery tip gradually from one just enough to blanch the epicardium to a red heat which caused charring. When, as frequently happened, a coronary vessel was severed by the cautery tip, hemostasis was achieved either by further cauterization or, in the case of larger vessels, by ligation. When cauterization was complete the appearance of the heart was identical with that illustrated in a previous article by Bakos.[3] Postmortem examinations revealed destruction of the entire right ventricular wall with the exception of variable patches on the endocardial layers. It was conservatively estimated that between 70 and 85 per cent of the entire wall was certainly destroyed in all successful experiments. In order to maintain an adequate venous return during this traumatic procedure a constant drip of normal saline was maintained through a femoral venous cannula at a rate of approximately 2 cc. per minute for the duration of the experiment.

In [s]tudying the response of the right ventricle to stress it was necessary to compare in the same animal [t]he reactions of the damaged ventricle with those [o]f the normal ventricle previous to cauterization. [I]nitial experiences indicated that, for this purpose, [t]he reactions to increasing venous input were difficult to quantitate. Consequently, the response to equivalent stresses of increasing pulmonary resistance was used. A screw clamp, so calibrated that it required 20 complete turns of a small wheel to go from a wide open to a closed position, was placed around the pulmonary artery just distal to the pulmonary valves. This clamp began to compress the artery at about eight turns and caused complete obstruction at about 18 turns of the wheel, depending on the size of the pulmonary artery. Progressive graded pulmonary artery occlusion to the point of frank decompensation was imposed in rigidly similar fashion both before and after traumatization of the right ventricle.

Results

Hemodynamic Effects. Fourteen technically successful experiments furnish the basis of this report. The effects of progressive cauterization on aortic and right ventricular pressure pulses are shown by segments of tracings in figure 1. Data of hemodynamic changes in another experiment are shown graphically in figure 2. The results of previous investigators were essentially substantiated. Progressive cauterization does not significantly alter the development of pressure in the right ventricle; the small changes observed are within the range of variation seen over several hours in normal hearts. Aortic pressures are reduced moderately at first, but recover even while cauterization is in progress. Femoral venous and right atrial pressure show very insignificant changes.

In table 1 are recorded the data from 12 experiments which furnished adequate data before and after cauterization. Thermal destruction of the right ventricle resulted in very small changes in aortic pressure. The average fall in systolic pressure was 9 mm. Hg, the changes ranging from −34 to +15 mm. Hg. Diastolic pressure fell an average of 10 mm. Hg, the changes ranging from −36 to +20 mm. Hg. Mean femoral venous pressure rose an average of 12 mm. saline with a range of −8 to +40 mm. The average rise in mean right atrial pressure was 16 mm. saline, with a range of 0 to +45 mm. Right ventricular diastolic pressure rose an average of 1.9 mm. Hg (27.1 mm. saline) with a range of 0 to +4 mm. Hg; while right ventricular systolic pressure increased an average of 2 mm. Hg with a range of −3 to +6 mm. Hg. These results on femoral venous and aortic pressures are also in substantial agreement with those reported by Starr,[1] although the range was somewhat wider in this larger series.

Myographic Changes in the Right Ventricle. In order to determine whether the right ventricular wall was contracting normally or, as it appeared visually, was expanding during systole after cauterization, simultaneous records of aortic pressure and of movements of the right ventricular wall were taken in five experiments. tion, as indicated by the drop of the curve at A-B. The lengthening is maintained until the end of systole, C, after which the fibers shorten, as indicated by the rise of the curve C-D. The typical shortening of the right ventricular wall seen in record *A* is converted to expansion after cauterization (*B*).

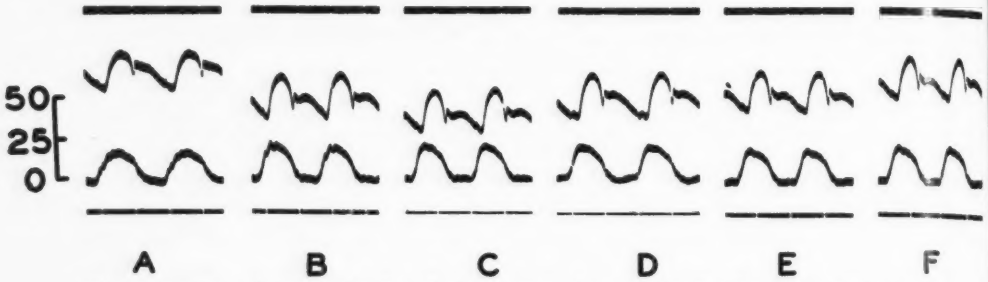

FIG. 1. Segments of records showing effects of progressive cauterization from the anterior to the lateral and then to the posterior surface of the right ventricle on aortic (upper) and right ventricular pressures (lower). *A*, control; *B*, 15 minutes; *C*, 30 minutes; *D*, 40 minutes; *E*, 65 minutes, and *F*, 75 minutes of electrocauterization. Note in *B* and *C* slight cardiac acceleration and decline of aortic pressure, increase in right ventricular diastolic and systolic pressures, with a steeper isometric contraction gradient, an earlier systolic peak, and slight relative abbreviation of systole. In *D*, *E*, F, despite increasing destruction of the right ventricular wall, aortic pressures return toward normal and right ventricular pressures show very slight changes. Postmortem estimate indicated that 70 to 80 per cent of the free right ventricular wall had been destroyed.

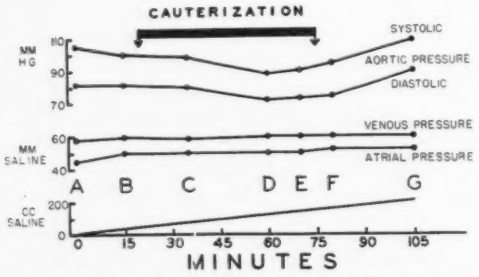

FIG. 2. Plot of hemodynamic data following progressive destruction of right ventricular wall. Slow continuous intravenous drip.

Figure 3 illustrates such recordings before (*A*) and after cauterization (*B*). With the onset of ventricular ejection the normal right ventricle shortens, as indicated by the rise of the curve A-B. This is maintained (B-C) until the ventricle fills in early diastole, when the ventricular fibers suddenly elongate, as indicated by the sharp fall of the curve C-D. After cauterization, on the contrary, the right ventricular muscle lengthens during systolic ejec-

Reactions to Stress of Increased Pulmonary Resistance. The responses of the right ventricle to equivalent increases of pulmonary resistance were studied in seven dogs. The curves reproduced in figure 4 show the nature of the responses before and after right ventricular damage. The control aortic pressure pulse (*A*) is of good contour with a diastolic pressure of 110, systolic pressure 138, and incisural pressure 125 mm. Hg. In a cycle length of .43 second the duration of systole is .24 second, giving an S/C ratio of .558. The corresponding right ventricular curve is of normal contour. The initial tension is 3 mm. Hg; the maximum pressure is 27 mm. Hg; and the S/C ratio is .535.

At 14 turns of the clamp wheel (*B*) there is no significant change in the aortic curve, diastolic pressure measuring 112, systolic 140, and incisural pressure 127 mm. Hg; the S/C ratio is .55. Initial tension in the right ventricle has now risen to 5 mm. Hg, and the maximum pressure generated is 48 mm. Hg. The S/C

ratio is .55. At 15 turns (*C*) aortic pressure is still well maintained, the respective pressures measuring diastolic, 107; systolic 128, and incisural 116 mm. Hg. The S/C ratio is now .538. In the right ventricle, although initial tension has remained at 5 mm. Hg, the maximum pressure has now reached 60 mm. Hg. The S/C ratio here, too, is now .538, which indicates an abbreviation of the contraction process. At 16 turns (*D*) pulsus alternans is noted in both curves. Aortic pressure has fallen to 82/68 mm. Hg, with incisural pressure 70 mm. Hg; and the S/C ratio is .516. The right ventricle shows its peak compensation with a pressure maximum of 78 after an initial tension of 7 mm. Hg: S/C ratio is .516, indicating further abridgement of systole. At $16\frac{3}{4}$ turns (*E*) aortic pressures are diastolic 18, systolic 32, and incisural 20 mm. Hg; the S/C ratio is .485. Right ventricular initial tension is 14, and the maximum pressure is 34 mm. Hg; S/C ratio is .457; i.e., systole continues to shorten. Fifteen minutes after the release of the pulmonary constriction (*F*), the pressure pulse curves have returned to normal configurations, aortic pressures measuring 108 mm. diastolic, 132 systolic, and 121 mm. Hg incisural pressure. The S/C ratio is now .55. The right ventricular curve, too, has returned to normal with

TABLE 1. *Pressure Changes following Right Ventricular Cauterization*

Dog	Estimated per cent Burn	Heart Rate		Femoral Venous Pressure (mean) (mm. saline)		Right Atrial Pressure (mean) (mm. saline)		Right Ventricular Pressure (mm. Hg)		Aortic Pressure (mm. Hg)	
		Before	After	Before	After	Before	After	Before	After	Before	After
6	60	139	132	20	30	10	28			107/72	80/40
9	60–70	165	161	70	110	50	95			130/95	145/95
10	90	226	214	60	52	48	48			130/106	100/70
11	75	221	183	60	65	40	60			105/70	118/90
16	75–80	174	174	60	60	50	52			100/82	108/90
18	75–80	183	175	75	100	50	65	26/0	23/2	124/97	95/63
20	70–80	176	188			25	35	20/0	24/2	153/127	139/113
21	50–60	160	209	55	65			20/0	26/4	143/114	144/121
22	70–80	147	176					23/3	28/6	132/108	130/102
23	80–90	196	181					36/2	34/2	133/104	120/90
24	80–90	180	173					26/4	23/5	139/115	135/114
25	75–85	204	214					20/3	24/4	138/120	117/102
Average	75	181	182	57	69	39	55	24/1.7	26/3.6	128/101	119/91
Range	50 to 90	139 to 226	132 to 214	20 to 75	30 to 110	10 to 50	28 to 95	20/0 to 36/4	23/2 to 34/6	100/72 to 153/127	80/40 to 145/121
Average change after burn		+1		+12		+16		2/1.9		−9/−10	
Range		−38 to +49		−8 to +40		0 to +40		−3/4 to 6/0		−34/20 to 15/−36	

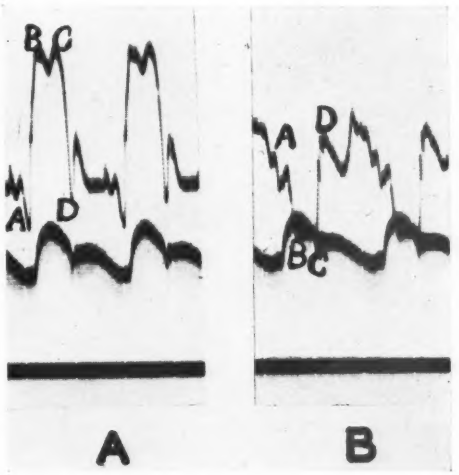

FIG. 3. Right ventricular myograms (upper) and aortic pressure (lower). *A*, normal control; *B*, after cauterization. Discussion in text.

a pressure of 23/3 mm. Hg, and the S/C ratio is raised to .60.

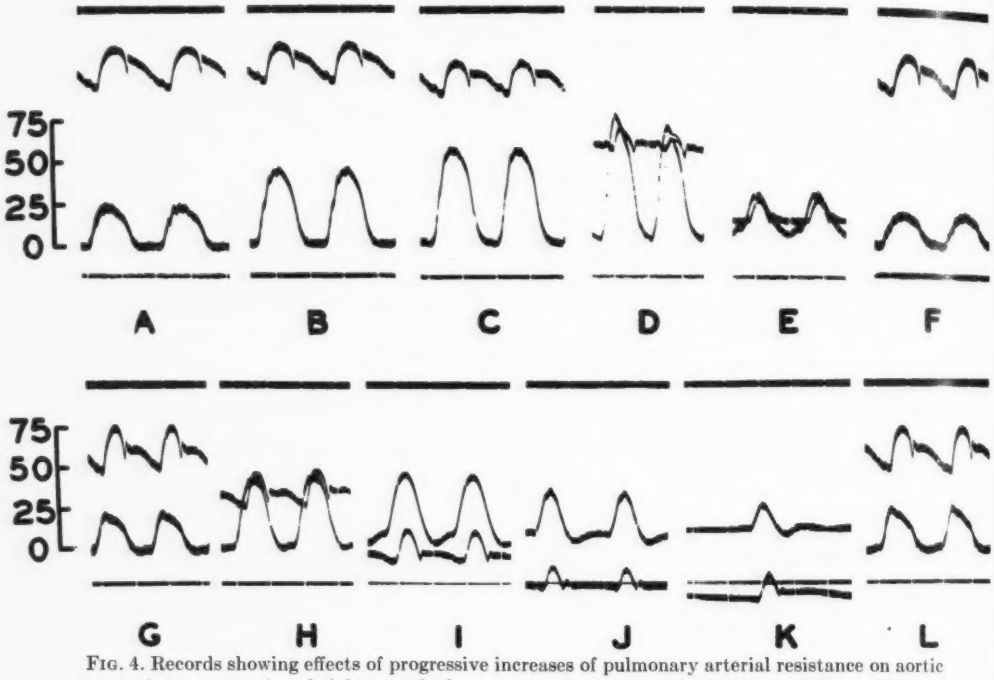

FIG. 4. Records showing effects of progressive increases of pulmonary arterial resistance on aortic pressure (upper curves) and right ventricular pressure (lower curves). Segments *A–F*, reactions of normal heart; segments *G–L*, reactions after cauterization. Discussion in text.

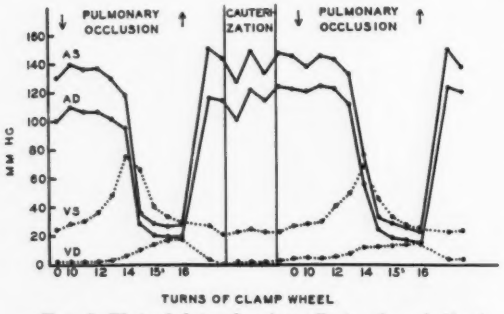

FIG. 5. Plot of data showing effects of equivalent progressive increase in pulmonary constriction in a normal heart and after cauterization of the right ventricle. AS, aortic systolic pressure; AD, aortic diastolic pressure; VS, right ventricular systolic pressure; DS, right ventricular diastolic pressure (initial tension). Discussion in text.

Following this test the right ventricle was cauterized. The detailed changes in the pressure pulses during cauterization are shown in the curves of figure 1. Curves *G* to *L* in figure 4 show the responses to the second application of progressive pulmonary constriction, 15 minutes after the completion of cauterization. The control aortic pressure curve (*G*) is relatively unchanged in contour, the pressures measuring diastolic 102, systolic 130, and incisural 116 mm. Hg; the S/C ratio is .53. The right ventricular curve shows the earlier systolic peak at 28 after an initial tension of 6 mm. Hg; the S/C ratio is .53. At 14 turns of the wheel (*H*), the aortic pulse contour remains normal, the pressures, however, having fallen to diastolic 78, systolic 102, and incisural 87 mm. Hg; the S/C ratio is .50. Right ventricular initial tension is 10 mm. Hg; systolic pressure is 50 mm. Hg; and the S/C ratio is .555. At 15 turns (*I*), aortic pressures have fallen to diastolic 38, systolic 60, and incisural 47 mm. Hg; the right ventricle has reached its peak response at a pressure of 55/15 mm. Hg and the S/C ratio for both chambers is reduced to

.45. At 16 turns (*J*) the aortic pressure readings are diastolic 18, systolic 34, and incisural 25 mm. Hg; the S/C ratio is .364. Right ventricular initial tension is 16, maximal tension 40 mm. Hg; its S/C ratio declines to .318. At 16¾ turns (*K*) at the height of decompensation the aortic pressures are diastolic 11, systolic 30, and incisural 21 mm. Hg; aortic S/C ratio has now fallen to .155. The right ventricular pressure is 33/19 mm. Hg; its S/C ratio is .136. The greater reduction in relative duration of systole after injury is obvious. Fifteen minutes after the release of pulmonary constriction (*L*), the pulse pressure curves have returned to preconstriction contours and measurements, the aortic pressures measuring diastolic 102, systolic 133, and incisural 120 mm. Hg; the right ventricular pressures measuring 30/5 mm. Hg. The S/C ratios are .487, that is, materially less than before the application of stress.

Comparison of aortic and right ventricular pressure pulses and S/C ratios at equivalent degrees of pulmonary resistance show that in this experiment the ability of the right ventricle to compensate was significantly reduced. Thus, in the normal ventricle aortic pressure was maintained in segment *B* through increase in left ventricular pressure, but fell considerably after cauterization, as shown in segment *H*. Again in segment *C*, the significant elevation of right ventricular pressure sufficed to reduce aortic pressure only to a slight degree, whereas in segment *I*, no further elevation of right ventricular pressure took place despite a marked elevation of diastolic pressure. The differential effects become very striking in comparison of segments *D* and *J*. Also, in the normal condition right ventricular pressure continued to rise until 16 turns of the wheel in segment *D*, whereas after cauterization no further increase took place with 15 turns of the wheel in segment *I*.

However, in several experiments the compensatory response of the damaged ventricle corresponded more nearly to the preceding response of the normal ventricle. Thus, in the experiment illustrated graphically in figure 5, aortic pressures both before and after cauterization began to decline after 12 turns of the clamp wheel, and the maximal elevation of right ventricular pressure took place with 14 turns of the wheel. The possibility that more viable muscle was present in the outer walls in these instances cannot be entirely excluded, despite careful postmortem checks of the damage. Nevertheless, the fact that nearly complete compensation was still possible after very extensive damage does raise the question as to the extent that muscular contractions of the free wall contribute to compensatory states in the normal heart.

Discussion

The results of previous investigators and their extension in this study, in a way, raise more questions than they answer. However, they give a clue as to possible faults in our methods of studying cardiac failure and may serve as a directive to future approaches.

The original observations of Starr and his associates that almost complete destruction of the right ventricular walls has little effect on arterial and peripheral venous pressures have again been completely confirmed. In addition, the increase in right atrial pressure and initial tension in the right ventricle, though somewhat more definite, is still of a low order of magnitude.

Starr and his associates used these observations as evidence that right heart failure, per se, cannot cause marked venous congestion. It becomes apparent from the studies of Bakos and the present observations that the procedure does not produce right heart failure, because destruction of the walls of the right ventricle spares a hidden subsidiary mechanism by which effective stroke volumes can be maintained through periodic elevation of right ventricular pressure. Consequently, it is highly doubtful whether the problem of right heart failure can be solved by any experimental procedure which inactivates or destroys only the outer walls of the right ventricle. The reason that experimental myocardial depression produced by chemical agents is generally associated with considerable elevation of central and peripheral venous pressures, whereas destruction of the right ventricular walls is not, may conceivably be found in the fact that the former also de-

presses a subsidiary contractile mechanism, while the latter procedure spares it.

Such considerations emphasize the importance of localizing the subsidiary contractile mechanism which is still able to elevate pressures in the right ventricle and pulmonary artery after destruction of the major portion of the right ventricular walls. Bakos[3] made the reasonable suggestion that contractile energy may be produced through a pull of ventricular muscle bundles upon inactive bands in the right ventricle, with which they are continuous. The idea was based on the architecture of the sinospiral and bulbospiral fibers which envelope the two ventricles. According to such a view, the pull exerted upon inactive right ventricular fibers during left ventricular systole should cause a shortening of the outer wall. However, myographic studies have shown that this does not occur; the right ventricular wall elongates during systole as a result of the elevation of intraventricular pressure created elsewhere. Furthermore, the concept implies that the systolic elevations of right ventricular pressure accord with the force of left ventricular contractions. This, however, is not the case; on the contrary, inverse relations occur when the right ventricle contracts against increased resistance. For example, in segments *H* and *I* of figure 4, the decline of aortic pressure and reduction of pulse pressure denotes diminished force of left ventricular contraction, while the right ventricular pressure reaches higher systolic levels. In other words, the activity of the damaged right ventricle is increased, while that of the normal left ventricle is reduced. Obviously, the activity of the two ventricles was maintained by separate mechanisms.

As an alternate mechanism, it could be suggested that the elevation of right ventricular pressure is produced through contraction of the interventricular septum, by shortening of the apex-base axis, by bulging into the right ventricle, or by a combination of these two effects. The results of the experiments presented are consistent with such an explanation only if we assume that septal contraction affects pressure in the right ventricular cavity, but not that in the left. Such a result is not impossible on an anatomic basis, but speculations are unwise. Experimental study of the behavior of the septum and its dynamic effects remains a challenge for future investigators.

Summary

1. The entire outer wall of the right ventricle of dogs was damaged as severely as possible by means of an electrothermocautery. This procedure caused a temporary slight fall in aortic pressure and a slight rise in peripheral and central venous pressures, and in right ventricular diastolic pressure during cauterization. The changes following 70 to 85 per cent destruction of the outer walls were of so low an order of magnitude as to lead to the conclusion that a normal, contractile right ventricular wall is not necessary for the maintenance of a normal circulation.

2. The reserve capacity of the damaged right ventricle was tested by the imposition of progressive, graded constriction of the pulmonary artery before and after thermal destruction of the outer right ventricular wall. The response to such imposed stress was impaired less than would be anticipated, indicating that even the reserve capacity of the right ventricle is not always reduced significantly by destruction of the external ventricular wall.

3. The results of this and other investigations indicate that right ventricular failure and venous congestion cannot be produced by extensive destruction of the outer ventricular walls, because a hidden mechanism is spared which is able to maintain approximately normal stroke volumes. The corollary follows that the dynamic effects of right heart failure cannot be studied by experimental procedures which inactivate or destroy only the outer walls of the right ventricle.

4. The subsidiary contractile mechanism which maintains efficient pumping action of the right ventricle after destruction of its outer walls has not been localized. The suggestion that the energy is derived from a pull of left ventricular muscle bands upon continuous but inactive bands of the right ventricle was not supported by experimental evidence. The ug-

gestion that contraction of the interventricular septum may be concerned still requires experimental validation.

ACKNOWLEDGMENTS

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The Effects of Increased Intracranial Pressure on the Pulmonary Circulation in Relation to Pulmonary Edema

By WILLIAM HARRISON, M.D., AND AVERILL A. LIEBOW, M.D.

Sudden elevation of intracranial pressure raises not only the systemic but also the pulmonary intravascular pressures, on occasion, sufficiently to result in pulmonary edema. At least two mechanisms are concerned, that of bradycardia, and that of left ventricular failure. Evidence is presented that interruption of vagal inflow temporarily abolishes the first mechanism. These observations are considered in relation to the clinical problem of head injury.

A CLASSIC experimental study of the effects of increased intracranial pressure upon the systemic arterial tension was published by Harvey Cushing[1, 2] some 50 years ago. More recently the observation that pulmonary edema often accompanies traumatic or spontaneous cerebral hemorrhage[3] has prompted an investigation of the consequences of increased intracranial tension for the lesser circulation. While the present work was in progress, the publications of Campbell and Visscher and their colleagues[4–6] appeared; the results of their studies will be compared with observations made in the course of the present work. The results of simpler experiments which have concerned themselves merely with the effect of a sudden rise of intracranial pressure in the production of pulmonary edema have been contradictory, those of Surtshin, Katz, and Rodbard[7] denying an association in the dog, while MacKay[8] claimed to have produced pulmonary edema within 30 seconds after applying a crushing trauma to the skull in the rat. Some of the contradictions may have to do with the divergent criteria that have been employed for judging the existence of pulmonary edema.

METHODS

In the present experiments dogs weighing 7 to 20 Kg. were employed under alpha-chloralose anesthesia (50 mg. per kilogram), supplemented before the intracranial pressure was raised by minimal doses of sodium Pentothal (sodium ethyl (1-methylbutyl) thiobarbiturate); after effectively raising tension within the skull, further anesthesia was usually not necessary. The choice of an anesthetic is important, for there is considerable evidence that deep narcosis may diminish the tendency to pulmonary edema.[9, 10] Chloralose seems to be chiefly a cerebral depressant and to interfere least with the cardiovascular reflexes.

The intracranial pressure, as well as the pressures in the pulmonary artery, left atrium, the femoral artery or aorta, and femoral vein were recorded optically by means of a bank of five Hamilton manometers. Polyethylene cannulas were placed in the systemic vessels and kept open by means of three-way stopcocks. Access to the lesser circulation was gained by applying plastic needle guides to the pulmonary artery and left atrium respectively by methods previously described,[11] at least eight days prior to the experiment. At this time the thoracic operative wound had healed and pressures on each side of the pulmonary circuit could easily be obtained by inserting long spinal needles from the manometers into the guides through the intact skin. These needles were kept patent by a constant slow saline drip through the side arm of a three-way stopcock.

Compression of the brain was achieved in various experiments by three different methods: (1) compression by means of a polyethylene bag, (2) introduction of Tyrode's solution under pressure intracisternally by means of a polyethylene catheter or large needle, and (3) introduction of Tyrode's solution subdurally. The bag compression method was first employed but was ultimately discarded. It was first attempted to place the bag epidurally or subdurally at a prior operation, but sufficient fibrous tissue was laid down to prevent the later effective expansion of the bag. The insertion of the bag on the day of the experiment was also unsatisfactory. It was possible to obtain adequate compression but the lateral displacement of the cerebrum and im-

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pacti n of the midbrain against the tentorium was consi ered to be an undesirable and unpredictable comp ication. Sudden death sometimes resulted after a ve slight increment of pressure within the bag, presu nably from herniation of the brain. That local press re upon the brain is not necessarily transmitted equa y to all parts of the cranial cavity was noted by C shing[1] in his early work. Fluid compression was inally used, therefore, by one of the two meth ds. This produced a more uniform compression but had the disadvantage of introducing additional fluid into the dog, sometimes in large quantity. The intra isternal introduction of the fluid with the needle, or even with the catheter, is fraught with the danger of damage to the brain during the introduction, or by some subsequent accident with displacement either into the cerebral substance, or out of the cisternal space. The most generally satisfactory was Cushing's[1] original method, whereby a 1 cm. button is trephined from the left vertex, the dura opened, and a tightly fitting threaded metal tube is screwed into the skull. Tyrode's solution is then forced through the tube to compress the cerebrum from a large pressure bottle regulated by a side-escape mercury valve. Pressure in the bottle is maintained at a level remarkably constant and regulable by keeping compressed air constantly bubbling through the escape valve. The pressure to which the solution is subjected is read on a mercury manometer, and recorded by means of one of the Hamilton manometers together with the four vascular pressures. At the end of each experiment of the cerebral compression type a needle is inserted into the cisterna magna to confirm free communication of pressure from vertex to the perimedullary space. Tyrode's solution at pH 7.4 was employed for the cerebral compression rather than saline, since in our experience saline at pH 7, when introduced into the subdural or subarachnoid space produced a progressive hyperpnea.

The experiments were performed with a tracheotomy tube in place, for it has been suggested that laryngospasm might lead to phases of inspiratory obstruction with a more negative intra-alveolar pressure that would favor the development of pulmonary edema, or phases of expiratory obstruction with a high intrathoracic pressure,[7, 12] and the tube furthermore effectively excluded the aspiration of saliva or other secretions from the pharynx.

Oxygen was administered during the course of some of the experiments, especially when there was marked bradycardia or bradypnea. Its use will be discussed.

Necropsies were performed within minutes after the death of the animal. The increase in weight of the lungs that may occur post mortem when they are allowed to remain in the thorax has been described by Burlacher.[13] The heart was promptly opened to confirm the position of the needles that had been left within their guides, and blood was aspirated into a suction bottle before it had clotted. It was seen that a tunnel of connective tissue had formed about the needle guides, with obliteration of the fissures between the left upper and lower lobes, and that there were tenuous fibrous adhesions in the region of the wound, but without generalized obliteration of the left pleural space or pericardial sac. The lungs were weighed together with a segment of trachea 5 cm. in length, and after dissecting away the left auricle, trunk of the pulmonary artery, and enlarged bronchial lymph nodes. The lung weight was expressed as a percentage of the body weight, the normal range except in the hot summer being 0.80 to 1.20.[14] The existence of congestion and edema was graded according to the following scale: Questionable: 1.20–1.40, Slight: 1.41–1.60, Moderate: 1.61–2.00, Severe: Above 2.01. Microscopic sections were made when the lung weights exceeded 1.20 per cent. Even in some of the heavier lungs, the presence of edema was indicated not by any large quantity of acidophilic coagulum within the alveoli, but by an increase in the width of the septa and in the perivascular and peribronchial collars of areolar tissue. Similar observations were made in this laboratory and elsewhere[15] of the pulmonary edema that follows the administration of alpha-naphthyl thiourea (ANTU) in the dog. Only rarely was bubbling fluid obvious in the bronchi and trachea of the dogs in the present experiment. Rales also may not be heard, despite obvious edema post mortem. Although the lung weight–body weight ratio is not an entirely satisfactory method of detecting pulmonary edema, it is by far the most objective. Gross examination is too easily susceptible to prejudice. When edema is present, there is loss of the pale salmon-pink color of the normal lung which is replaced by dull red-grey, less spongy and resilient, doughy noncrepitant tissue. These changes were first apparent chiefly in the dependent portions of the lungs near the hilum, especially on the medial aspects. Obviously, a contribution to any increase in the weight of the lungs may be made by a greater content of blood. In the technic of preparation, almost all of the blood is removed from the larger vessels which are thus left in the collapsed state. In retrospect, perhaps the best method to separate the contribution made by the two would be to measure the increase in iron content in relation to the increase in total weight of the lung above normal.

Since it is clear from the experiments of Cushing that increased intracranial pressure stimulates both the parasympathetic and sympathetic mechanisms, the effects of atropinization and cervical vagotomy in altering the response to the cerebral compression were examined. In addition, the effects of bilateral cervical vagotomy alone were observed without cerebral compression as in Farber's[16, 17] experiments. In this last group the amount of parenteral fluid was purposely varied. Two dogs received abundant saline, approximately 100 cc. per kilogram per hour,

while in three others saline was administered in smaller amounts.

Observations

Effects of Raising Intracranial Pressure

The sequence of events when the intracranial pressure is rapidly raised may be illustrated in an experiment (serial No. 4, table 1) in which a subdural bag was rapidly expanded (fig. 1). In this experiment attempts had been made unsuccessfully for some hours to increase the intracranial pressure by expanding a polyethylene bag which had been placed epidurally at a previous operation. This bag was then removed and another polyethylene bag was inserted beneath the dura which was sewn over it. Control records were obtained (fig. 1, sect. 1). Water under pressure controlled manometrically was then introduced into the bag. A detailed protocol of the experiment follows:

6:07 p.m. (fig. 1, sect. 1) With the bag uninflated the femoral artery pressure varied between 192/95 and 192/78 mm. Hg; the mean left atrial pressure was 11.5 cm. H_2O, and the pulmonary artery pressure 46/10 to 51/16 cm. H_2O.

6:20 p.m. (fig. 1, sect. 2) Bag pressure to 120 mm. Hg. Femoral artery pressure rose at once to 200/100–128, but without significant change in left atrial and pulmonary artery pressure.

6:40 p.m. (fig. 1, sect. 3) Bag pressure to 160 mm. Hg. Within 10 seconds bradycardia appeared, during which the heart rate fell to 36, but there were alternating phases during which the heart rate accelerated to 72 for three or four beats. During the slow beats the systemic diastolic pressure was very low (30) and the pulse pressure was very large (systolic 174); as the heart accelerated the diastolic pressure rose to approximately 100 while the systolic remained the same. During these cycles the respirations were also slow. As Campbell and co-workers have described, at the onset of bradycardia the left atrial pressure rose at once, in this instance to a mean of 21 with an accompanying rise in the pulmonary artery pressure.

Table 1.—*Factors in Development of Pulmonary Edema*

Serial No.	Body Weight	Length of Experiment	Parenteral Fluid	$\frac{\text{L.W.}}{\text{B.W.}} \times 100$
		Supratentorial Bag Compression		
	kg.	*hrs.*	*cc./kg./hr.*	
1	15.9	3.5	16	1.00
2	13.2	4.7	23*	1.00
3	10.4	3.0	76*	1.20
4	12.2	7.0	24*	1.46
		Cisternal Fluid Compression		
5	10.0	3.0	76*	.91
6	16.8	3.5	26	.94
7	19.9	7.5	30*	.97
8	17.7	5.0	34*	1.00
9	10.9	2.5	57*	1.04
10	10.7	5.7	28*	1.30
11	15.9	7.0	19*	2.71
		Supratentorial Fluid Compression		
12	12.5	7.7	38	.95
13	16.6	3.7	50	.97
14	10.9	4.7		.98
15	10.4	2.7	56	1.01
16	13.6	6.5	28	1.04
17	15.2	6.2	52	1.04
18	13.6	2.2	50	1.11
19	12.2	7.5	47	1.25
20	15.1	1.7	49	1.29
		Supratentorial Fluid Compression + Atropine		
21	13.5	2.0	58*	.99
22	17.9	3.0	37	1.04
23	9.1	5.0	59	1.08
24	12.2	5.5	55	1.12
25	10.0	2.0	65	1.19
26	8.6	1.0	79*	1.23
27	9.3	2.5	71*	1.73
28	15.9	3.5	107	2.20

Table 1.—(*Continued*)

		Supratentorial Fluid Compression + Vagotomy		
29	12.7	5.5	37	.95
30	20.4	8.0	22	1.45
31	10.7	4.7	89	1.91
		Vagotomy		
32	20.8	5.0	6	.59
33	9.8	5.5	7	1.18
34	16.6	5.0	64	1.12
35	12.5	5.2	94	2.20
36	7.7	5.0	132	2.30

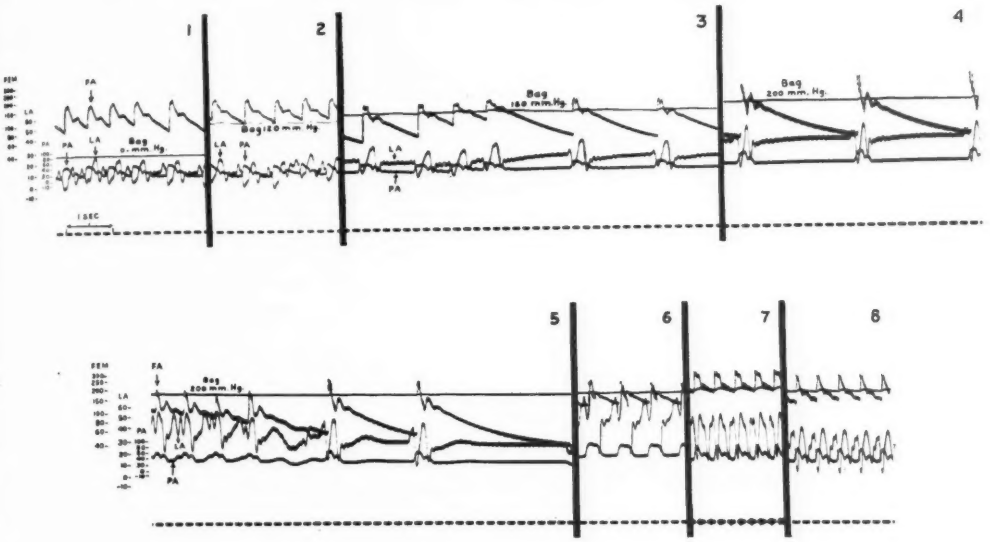
* Indicates estimate based on average saline inflow into cannulas of 5 cc./min., and, where applicable, on rate of inflow in drops per min. of Tyrode's solution used for cerebral compression (1 drop of Tyrode considered = 0.05 cc.).

7:00 p.m. (fig. 1, sect. 4) With a further increase in the pressure within the bag to 200 mm. Hg, the systemic arterial pressure ranged in the neighborhood of 200/38 and there was bradycardia associated with a continued rise in the mean left atrial pressure to 32.

7:12 p.m. (fig. 1, sect. 5) Bursts of tachycardia with systemic pressure falling, followed by apnea. Pressures in lesser circulation remained elevated.

7:14 p.m. (fig. 1, sect. 6) Sudden tachycardia, systemic pressure rose to 240/132 and left atrial pressure to a mean of 51. Mean pulmonary artery pressure was 60.

7:20 p.m. Dog going into shock. Dead at 7:26 p.m.



EFFECTS OF INCREASED INTRACRANIAL PRESSURE ON CIRCULATION

FIG. 1. Effects of increased intracranial pressure on circulation.

This animal was exceptional, in exhibiting no obvious pulmonary edema, although the mean left atrial pressure was maintained above 20 cm. H_2O for approximately 30 minutes, with levels momentarily reaching 51.

In the present experiment there are demonstrated two phases in the elevation of the left atrial pressure. One is immediately consequent upon the induction of bradycardia. The other occurs late, in association with an extreme rise in systemic arterial pressure, and is presumably the result of incipient failure of the left heart. In some instances there is a slight rise in the mean left atrial pressure even before the bradycardia appears, particularly when there is a large elevation of the aortic pressure.

The sequence of pressure changes was similar by whatever means the intracranial pressure was increased. With fluid compression there was less delay than with the subdural bag, the pressure on the medulla could be accurately controlled, and sudden fatal herniation of the brain was avoided. Bradycardia, and sometimes apnea, was observed in these experiments with a rapid rise in intracranial pressure to levels that varied between 100 and 150 mm. Hg. with different animals. When the rise in intracranial pressure was very gradual, bradycardia and apnea could be avoided, while the systemic pressure rose gradually in accomodation as described by Cushing.[1, 2] The rise in the left atrial pressure was then in association with the second phase described above.

The systemic venous pressure, recorded in most of the fluid compression experiments was observed to rise relatively slightly. This is in contrast to the result when fluids are rapidly

introduced intravenously.[18, 19] Under these circumstances, also, the left atrial pressure can be made to rise to high levels, but this is accompanied by a rise in the systemic venous pressure; it is remarkable that here the pressure in the left atrium rose much higher than in the femoral vein, as in the observation made by Yeomans, Porter and Swank,[18] and in our own observations.[20] This is probably the result of the relative indistensibility of the left atriovenous system.[21]

In summary of these observations, it may be said that edema of the lung, as measured by the objective criterion of lung weight in proportion to body weight was only occasionally produced by any of the three methods when neither atropine nor vagotomy had been instituted (table 2). In three of 20 experiments there was questionable edema, in one edema was slight, and in only one other, where the experiment had been carried on for seven hours, was the edema severe.

TABLE 2.—*Lung Weight as Percentage of Body Weight in Dogs with Elevated Intracranial Pressures*

Method of Increasing Intracranial Pressure	Total Number	L.W./B.W. × 100				
		1.	1.20-1.40 (Questionable)	1.41-1.60 (slight)	1.61-2.00 (Moderate)	> 2.01 (Severe)
Subdural Bag...	4	3		1		
Cisternal Fluid.	7	5	1			1
Supratentorial Fluid.....	9	7	2			
Supratentorial Fluid + Atropine.....	8	5	1		1	1
Supratentorial Fluid + Vagotomy.....	3	1		1	1	
Vagotomy.....	5	3				2

* Degree of "edema."

Effects of Atropinization and Vagotomy

Since the induction of bradycardia consequent to the elevation of the intracranial pressure appeared to be one of the mechanisms associated with an immediate rise in the left atrial pressure, it was considered of interest to observe the effects of interrupting the vagal pathways either with atropine or by low cervical vagotomy. Observations made during a typical atropinization experiment (serial No. 27, table 1) will now be detailed.

10:23 a.m. Dog 165. Weight 9.3 Kg. Systemic arterial blood sample taken: Oxygen saturation 99.2 per cent. Animal then anesthetized with 20 cc. chloralose, 25 mg. per cc., intravenously.

10:30 a.m. 3 cc. of 2 per cent sodium Pentothal given intravenously. Cannulation of arterial and venous systems of greater and lesser circulation performed. Tracheal tube placed.

11:27 a.m. Systemic arterial blood sample: Oxygen saturation 94.4 per cent. Head trephined and connected to pressure system.

12:33 p.m. Control record: Femoral artery pressure 168/134 mm. Hg; mean left atrial pressure 1 mm. Hg; mean pulmonary artery pressure 11 mm Hg; mean femoral vein pressure 3 mm. Hg. Dog hereafter on continuous oxygen at atmospheric pressure, via intratracheal tubes.

12:34 p.m. Intracranial pressure raised to 100 mm. Hg.

12:44 p.m. Intracranial pressure raised to 110 mm. Hg. Femoral artery pressure now 211/148 without significant changes in the other pressures.

12:49 p.m. Intracranial pressure raised to 120 mm. Hg. Four minutes after the rise, systemic pressure was 220/148; other pressures approximately the same as before.

12:54 p.m. Intracranial pressure raised to 133 mm. Hg. The animal now showed a leakage of fluid from the nose and the eyes were protuberant. Almost immediately after this last rise in intracranial pressure there was an irregular slowing of the heart as in fig. 1, sect. 3, with swings in the femoral diastolic pressure and an increase in the left atrial pressure. Bradycardia then became established.

1:01 p.m. The animal suddenly became apneic. During the next two minutes the heart rate was 48, the femoral artery pressure approximately 200/97, and the left atrial pressure became elevated to approximately 10 mm. Hg, while the mean pulmonary artery pressure was 12 and the femoral vein pressure had a mean of 6.

1:03 p.m. Atropine 0.6 mg. administered intravenously. The sequence of events is shown in a record reproduced in figure 2. Thirty seconds after the administration of the drug the aortic diastolic and systolic pressures began to rise, accompanied by a transient rise in the pressures in the lesser circulation. Tachycardia (approximately 160) then occurred. Between 30 and 35 seconds after the atropine the first spontaneous respiration occurred indicated by the dip in the curves for the left atrial and pulmonary arterial pressures, following which the pressures in the lesser circulation

decreased while the femoral artery pressure was maintained at the very high level of 260/160. The femoral artery pressure elevated before the administration of atropine fell as soon as the atropine effect became manifest, and while the pressures in lesser circulation were still high.

1:12 p.m. Femoral artery pressure 222/144; left atrial pressure 1; femoral vein pressure 3.

1:13 p.m. Intracranial pressure raised to 135.

1:17 p.m. Femoral artery pressure 234/152–240/170. Atropine, 0.6 mg., administered intravenously.

1:30 p.m. Intracranial pressure raised to 145.

1:40 p.m. Intracranial pressure raised to 155.

1:42 p.m. Pronounced Traube-Hering waves.

1:50 p.m. Respirations irregular with periods of apnea lasting as long as one minute.

2:04 p.m. Pronounced Traube-Hering waves with peaks at 271/193 and troughs at 193/120. Respirations irregular. Atropine, 0.6 mg., administered intravenously.

2:25 p.m. Intracranial pressure elevated to 165. The sequence of events following this last rise is indicated in the record reproduced in figure 3. The portions of records taken at 2:28 p.m., 2:39 p.m., 2:45 p.m., and 2:55 p.m. (30 minutes after the last rise in intracranial pressure) are shown. The first two records are divided into two parts, at the troughs and peaks of the Traube-Hering waves. It will be noted that pulsatile variations in the intracranial pressure were more prominent at the peaks of the Traube-Hering waves. At the peaks of these waves of systemic hypertension, the pressures in the lesser circulation tended to be high, but were not always in phase. There was, nevertheless, a general upward trend in the latter reaching and maintaining high levels between 14 and 20 minutes after the last rise in intracranial pressure until a terminal phase 10 minutes later.

2:30 p.m. Systemic arterial blood sample: Oxygen saturation 109.5 per cent in reference to hemoglobin.

2:55 p.m. Animal suddenly went into shock with a fall in the systemic arterial pressure and died a few minutes later. It is interesting to note during this last phase that all pressures were sagging, except that in the femoral vein which was rising and exhibiting a pronounced pulse. In this animal the lung weight–body weight ratio × 100 = 1.73.

At the end of the experiment a needle was introduced into the cisterna magna and it was demonstrated by simultaneous records that the intracisternal pressure followed closely the level of the intracranial pressure as measured in the manometer connected to the Tyrode bottle and supratentorial trephine opening. This indicated free communication of pressure above the tentorium with the perimedullary cistern. In this experiment there was a moderate degree of pulmonary edema with a lung weight–body weight percentage of 1.73.

In each of seven experiments in which either atropine or vagotomy was employed the effects were similar. With the appearance of severe bradycardia and apnea the precedure rapidly restored respiration and there was a sudden tachycardia with high systolic and diastolic pressures, while the pressures in the lesser circulation quickly fell. It then became possible to raise the intracranial pressure to much

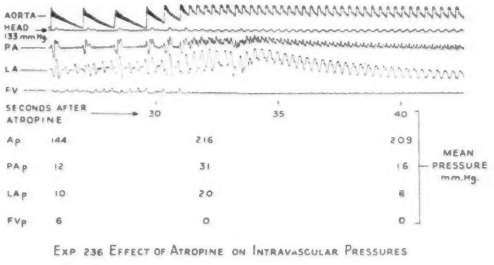


FIG. 2. Effect of atropine on intravascular pressures.

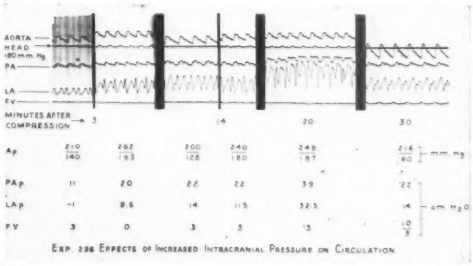


FIG. 3. Vascular pressures in atropinized dog after cerebral compression.

higher levels (30 or more mm. Hg higher than before). Ultimately, however, there was evidence of failure of the left ventricle with a rise in the left atrial pressure.

Relation of Lung Weight–Body Weight Ratio to Pressure in the Left Auricle

It might be expected from observations of capillaries elsewhere that as the capillary pressure approached the onchotic pressure, exudation of fluid would be favored.

All nine dogs in the fluid compression experiments (table 1, serial Nos. 5–31) in whom

the lung weight exceeded 1.20 per cent of the body weight, induced elevations of the mean left atrial pressure in excess of 20 cm. H_2O had existed for at least 15 minutes, with capillary pressure slightly in excess of this level. In the 18 dogs with normal lung weight–body weight ratios, four had mean left atrial pressures above 20 cm. H_2O at some time. In the bag compression experiments all four animals before death showed at least transitory elevation of the left atrial pressure above 20 cm. H_2O. Usually this was terminal and was associated with the cerebral herniation that has been described. In one animal (serial No. 1, table 1), there was no pulmonary edema despite a left atrial pressure exceeding this level which had been maintained for approximately 25 minutes. Likewise in the report of Campbell and his colleagues[5] not all animals with high left atrial pressure exhibited pulmonary edema.

TABLE 3.—*Use of Oxygen in Relation to Lung Weight–Body Weight Ratio*

L.W.-B.W. × 100	O_2 Used	O_2 Not Used
<1.20	4	17
>1.20	5	5

Role of Infused Fluids

Control experiments to be reported in detail elsewhere[20] in which Tyrode solution and saline were injected for a five hour period demonstrated that no more than questionable edema was produced when the injection rate was less than 80 cc. per kilogram per hour, and that even at rates as great as 100 cc. there might be no increase in lung weight above 1.20 per cent of body weight, although usually in the five hour period moderate or severe pulmonary edema was produced. At the rates of infusions prevailing in the cerebral compression, one might expect from observations of this control series a drop in the hematocrit of 10 to 20 per cent toward the end of a five hour period of observation. As shown by Yeomans, Porter and Swank,[22] there would be a comparable fall in the serum protein with a drop in onchotic pressure of 2.5 to 5 mm. Hg.

Role of Vagotomy

There has been controversy concerning the role of vagotomy in itself as a possible mechanism in the production of pulmonary edema. Farber[16] in experiments upon guinea pigs reported development of pulmonary edema after vagotomy alone, but in a subsequent report[17] detailing similar experiments in rabbits it was found that large quantities of fluid were necessary in addition to the vagotomy. In the present series it appeared that edema developed in dogs five to five and one-half hours after vagotomy only if a saline inflow approaching 100 cc. per kilogram per minute were administered (table 1, serial Nos. 32 to 36).

Relation of Pulmonary Edema to the Administration of Oxygen. Oxygen was used in some of the experiments and did not prevent the development of pulmonary edema, as shown in table 3, which summarizes the data from serial Nos. 1–31 (table 1). It is obvious in fact that oxygen was used more frequently in those animals which ultimately developed pulmonary edema, in order to counteract the effects of the extreme bradycardia and bradypnea characteristic of the course in these animals. Thus, the oxygen helped to keep these animals alive for an interval sufficiently long to permit the development of pulmonary edema associated with the pressure changes in the lesser circulation.

Observations on Oxygen Saturation of the Systemic Arterial Blood. It is stated that in the peripheral capillary bed anoxia is a factor favoring extravasation of fluid. Although relatively little is known of the influence of anoxia on the capillaries of the lung, this factor should nevertheless be considered in evaluating mechanisms of pulmonary edema.

In contrast with the severe anoxia that follows deep Pentobarbital anesthesia, the methods used in the present series of experiments proved superior. Under chloralose alone, in 12 observations, the oxygen saturation was found to vary between 93 and 100 per cent. With the sodium Pentothal supplement the oxygen saturation in observations on six dogs was found to be as low as 89.6 per cent in one experiment, but above 90 per cent in all

others. As a rule the oxygen saturation fell less than 5 volumes per cent after the sodium Pentothal supplement, while the animal was breathing air. With oxygen breathing, the oxygen saturation before the development of pulmonary edema was usually in excess of 100 per cent in relation to hemoglobin, rising as high as 110.6 per cent in one instance.

Six determinations of oxygen saturation made within one half hour before death of the animals are summarized in table 4. In three animals, those with the highest lung weight–body weight ratios, there was some reduction in oxygen saturation. It is evident that anoxia was severe in but one animal, serial No. 36. It was, however, greater than the recorded value

TABLE 4.—*Oxygen Saturation of Systemic Arterial Blood in Relation to Lung Weight–Body Weight Ratio*

Serial No.*	O_2 Administered†	Time of O_2 Sample before Death	O_2 Sat.	L.W./B.W. × 100
		min.	%	
32	+	11	101.4	.59
34	−	30	100.0	1.12
27	+	25	109.5	1.73
31	+	5	88.0	1.91
35	−	20	90.0	2.20
36	−	5	>34.3	2.30

* Serial numbers, as in table 1.

† + = Animal on O_2; − = Animal breathing room air.

of 34.3 per cent saturation since this animal had received an enormous volume of fluid, 132 cc. per kilogram of body weight per hour for a five hour period, which would reduce the carbon monoxide capacity by about one half. In the calculation, the carbon monoxide capacity of the original preinfusion blood sample only was used, since the postinfusion capacity was not available.

Discussion

These observations lead to conclusions different from those of Campbell and his associates, in that pulmonary edema was only occasionally produced in the dog upon raising the intracranial pressure. The conditions of the experiment differed in that they employed sodium pentobarbital anesthesia, in the use of a balloon for increasing the intracranial pressure, and in other details. In the Minnesota report, moreover, the weights of the lungs in relation to the body weight were not given and the less objective criteria of gross and microscopic observation were the standards of measurement of the pulmonary edema. Nevertheless, in both series of observations it was possible to demonstrate an elevation of pulmonary capillary pressure, thereby establishing conditions favorable to the development of pulmonary edema. In the present experiments it was demonstrated that the left auricular pressure would become elevated not only in immediate association with bradycardia, but also after the heart had been caused to labor against the extreme hypertension produced by raising the intracranial pressure to high levels so slowly that bradycardia was avoided.

The immediate life-saving effect of atropine in interrupting parasympathetic inflow was apparent in the present observations, as in those of Campbell and his associates. In addition it was found that the animals would now tolerate an additional increment of 30 mm. Hg or more above that which had previously produced apnea and bradycardia, but that ultimately there was cardiac failure with a renewed increase in left atrial pressure with associated pulmonary edema. Thus, if the effect in patients is the same as in these experimental animals, atropine may provide a period of grace during which operative intervention may relieve the rising intracranial pressure.

As the gap between the capillary blood pressure in the lungs and the protein onchotic pressure becomes narrowed, it is obvious that additional factors tending to narrow this gap should be avoided. Among these factors are excessive infusion of fluids, especially of hypertonic crystalloids, or protein-containing solutions, and any reduction in intra-alveolar pressure such as might be associated with obstruction of the respiratory tract. In fact, tracheotomy has been suggested in the management of severe head injuries where unconsciousness is likely to persist for more than 24 hours.[12]

Summary and Conclusions

Study of the systemic and pulmonary intravascular pressures in dogs suggests the existence of a cardiopulmonary factor in the mechanism of death. A striking rise in the pressure within the left atrium may occur by two mechanisms (1) in immediate association with bradycardia as the intracranial pressure is elevated to levels ranging between 100 and 150 mm. Hg; (2) later, in association with an immense systemic hypertension resulting in accomodation to the rising intracranial pressure, even when this is so slow that bradycardia and apnea are avoided. Atropine, by interrupting bradycardia and apnea, permits an additional increment of intracranial pressure of 30 mm. Hg or more, but ultimately the left atrial pressure becomes elevated. Thus, the atropine provides a period of grace for adopting measures designed to lower intracranial pressure. As judged by the objective criteria of the ratio of lung weight to body weight, pulmonary edema is only occasionally produced, but especially in those animals where the left atrial pressure is maintained above 20 cm. H_2O for more than 15 minutes. Nevertheless, as the margin between pulmonary intracapillary and onchotic pressure is reduced in consequence of the altered hemodynamics associated with cerebral compression, quantitative factors involving parenteral fluid, and intra-alveolar pressure become increasingly important.

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Clinical Evaluation of 1-Hydrazinophthalazine (C-5968) in Hypertension

With Special Reference to Alternating Treatment With Hexamethonium

By Captain Robert L. Johnson, M.C.,U.S.A.F., Edward D. Freis, M.D., and Harold W. Schnaper, M.D.

Single oral doses of 1-hydrazinophthalazine frequently lowered blood pressure particularly diastolic pressure in hypertensive patients. Prolonged therapy was less successful, apparently as a result of development of tolerance or side effects. The best long-term results were obtained when 1-hydrazinophthalazine was alternated with hexamethonium.

In 1950 Gross, Druey and Meier[1] reported on the action of a group of phthalazine derivatives including 1-hydrazinophthalazine (C-5968) which were found to depress blood pressure in animals. This was confirmed by other investigators.[2–5] In contrast to the effect of other vasodilating agents, these phthalazine compounds increased renal blood flow in animals as measured by Rein's thermostrohmuhr. Reubi[6] demonstrated in man that 1-hydrazinophthalazine (C-5968) produced a constant increase in renal blood flow in association with a diminished renal resistance and a variable reduction in blood pressure. Since this drug has been reported to possess these properties it seemed of interest to assess the value of the drug in the treatment of essential hypertension.

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Immediate Hypotensive Effects of an Oral Dose

The hypotensive response to 1-hydrazinophthalazine administered parenterally has been discussed in a previous communication.[7] To determine the immediate effects of oral administration the drug was given to hospitalized patients after allowing sufficient time for stabilization of blood pressure. The initial dose was 50 mg., but if this amount failed to produce a significant hypotensive response or side-effects, the dosage was increased after 24 hours or longer by 50 mg. increments until a definite response was obtained.

Sixteen hypertensive patients were studied (table 1). Following ingestion of 1-hydrazinophthalazine the reduction of systolic blood pressure in the entire group averaged 10 per cent (range 0 to 32 per cent) in the supine position and 21 per cent (range 4 to 42 per cent) in the erect position. The depression of diastolic blood pressure averaged 16 per cent (range 4 to 42 per cent) in the supine position and 24 per cent (range 4 to 50 per cent) in the erect position for the entire group. Thus, the percentile reduction was greater in diastolic pressure than in systolic.

Six of these patients were given only 50 mg. of 1-hydrazinophthalazine because of minor side effects, and it is probable that further re-

duction of blood pressure could have been obtained with larger dosages. Conversely two of the five patients given 150 mg. of the drug exhibited reductions of less than 15 per cent in both the erect and supine positions.

The onset of action usually appeared within 20 to 30 minutes, reached a maximum between 30 and 120 minutes and usually disappeared after two to four hours. However, when dosages approached toxic levels, marked reductions of blood pressure occurred and evidence of drug activity persisted for as long as eight or even 12 hours.

significant reduction of blood pressure. In these patients dosages had been increased from 50 mg. two to four times daily to 124 or 150 mg. two to four times daily.

Six patients exhibited a significant hypotensive effect in the early period of treatment which, however, became less and less marked despite elevation of dosage. The following case illustrates this apparent development of tolerance.

J. J., a Negro man, age 52, with hypertension known for one year, entered the hospital because of congestive heart failure. The nonprotein nitrogen

TABLE 1.—*The Effect of Acute Doses of C-5968 in Hypertensive Patients*

Pt.	Dose mg.	Arterial Pressure mm. Hg				Duration of Effect *Hours*	Side Effects
		Control		After C-5968			
		Supine	Erect	Supine	Erect		
S. L.	50	220/120	230/130	198/100	175/105	2	None
E. S.	100	152/95	142/100	140/90	130/80	3	None
C. L.	50	162/90	150/90	145/82	115/75	3	None
R. M.	100	150/115	170/130	150/110	145/110	3	None
R. D.	150	212/130	212/125	205/125	185/120	1½	None
M. K.	50	170/106		156/96		2	None
F. J.	50	235/130		200/110		2	None
L. S.	150	185/115		164/94		4	None
W. C.	150	170/90	160/95	170/84	138/72	3	Severe headache, marked palpitation
M. M.	100	250/155	240/160	170/90	140/80	12	Severe headache, weak and faint, visual blurring
J. D.	150	210/130	200/130	190/90	118/82	10	Severe headache
B. F.	50	190/108		180/92		3	Mild headache
W. H.	100	194/138	185/132	156/96	150/92	3	Weak and faint
L. F.	150	262/158	250/162	235/140	240/140	4	Weak and faint
W. P.	150	215/120	225/140	175/85	154/80	6	Weak and faint
M. S.	50	202/140	210/144	190/120	204/114	4	Palpitation

EFFECT OF CONTINUOUS ORAL ADMINISTRATION OF 1-HYDRAZINOPHTHALAZINE

Seventeen patients were treated continuously with 1-hydrazinophthalazine. All except two were outpatients. Of this number eight failed to exhibit a satisfactory response to the drug. Four developed either severe headache or palpitation after several days of treatment with 50 mg. of 1-hydrazinophthalazine two to four times per day. The headache was of sufficient severity so that the patients refused further medication. The remaining four patients were under treatment for periods ranging from two weeks to three and one-half months without

was 90 mg. per 100 cc. Congestion cleared following the use of digitalis, mercurial diuretics and salt restriction, but the nonprotein nitrogen remained elevated. During one month of hospitalization under no specific hypotensive therapy the average blood pressure was 215/135.

He was readmitted to the hospital six weeks after the previous discharge for a trial of 1-hydrazinophthalazine. The blood pressure was 215/145. The optic fundi exhibited grade III hypertensive changes. The nonprotein nitrogen was 95 mg. per 100 cc. and cardiomegaly was still present, but without signs of congestive failure.

During five days of treatment with the Kempner rice and fruit diet,[8] the blood pressure ranged from 195/125 to 220/160 and averaged 200/140 (fig. 1). An initial dosage level of 25 mg. of 1-hydrazi-

nopt[illegible]alazine three times per day resulted in a decrease of diastolic pressure to 125 mm. Hg. The next day each dose was increased to 50 mg. with a further fall in diastolic blood pressure to 110 mm. Hg. However, over a period of four days the diastolic pressure rose gradually to a level of 130 mm. Hg (fig. 1). On the seventh day of treatment with C-5968 the dosages were increased to 75 mg. three times per day; this again was followed immediately by a reduction of diastolic blood pressure to 110 mm. Hg, but by the ninth day the diastolic pressure again rose to a level of 140 mm. Hg. Again the dosage was raised to 100 mg. and again the diastolic pressure fell slightly to 125 mm. Hg for the succeeding two days. The dose was then increased to 125 mg. on the twelfth day of treatment with 1-hydrazinophthalazine but the diastolic blood pressure remained at a level of 130 mm. Hg. The nonprotein nitrogen was unchanged.

Tolerance developed more quickly in this case than in most patients who exhibited a significant hypotensive effect initially. However, in this case as in the others the tolerance was not permanent since the drug was discontinued for one week and begun again in low dosage with hypotensive effect but with a repetition of the cycle of rapidly developing tolerance as observed during the first treatment period with 1-hydrazinophthalazine.

Three of the 17 patients apparently maintained sustained hypotensive effects while under treatment with 1-hydrazinophthalazine. All three of these cases were given the drug only twice daily. This wide spacing of doses may account in part for the apparent lack of tolerance. The following case is illustrative.

L. C., a 35 year old Negro woman had moderate essential hypertension of two years' duration. During two months of treatment with phenobarbital and a low salt diet, the blood pressure during eight visits to the outpatient department averaged 165/110 sitting and 155/115 erect. On the first visit after two weeks of treatment with 50 mg. of 1-hydrazinophthalazine twice daily the blood pressure was 135/85 sitting and 125/90 erect. Over the following seven months, while taking the same dose of 1-hydrazinophthalazine, the blood pressure during nine visits averaged 140/95 sitting and 135/95 erect. At the middle of this seven-month period while on placebos for two weeks, the blood pressure during two visits averaged 155/110 in the sitting position and 150/115 while standing.

Two of the six patients who had exhibited hypotensive responses only during the early period of treatment with 1-hydrazinophthalazine also had severe renal disease with chronic uremia. In neither of these was there evidence of improvement in renal function as judged by the degree of nitrogen retention, albuminuria and the urinary sediment. Three patients with only mild renal involvement, one of which showed a sustained hypotensive response to 1-hydrazinophthalazine and two a hypotensive response only during the early phase of treatment, reported a decrease in nocturia after two to four weeks of treatment.

Side Effects

Four of the 16 patients who were given single doses of 1-hydrazinophthalazine developed headaches which were severe in three

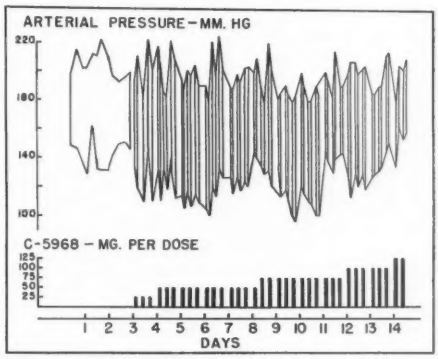

Fig. 1. Chart of the arterial pressure and dosages of 1-hydrazinophthalazine in J. J., a Negro man, age 52, with essential hypertension showing development of tolerance to increasing doses of this drug. See text for further details.

patients. The headache usually centered in the occipital area and was described as being grinding and pounding in character. It usually lasted four to six hours and did not respond to aspirin or caffeine. It always was accompanied by a definite hypotensive effect and occurred after doses varying from 50 to 150 mg.

During regular administration, when dosages were elevated rapidly and at short intervals of four to six hours, headache appeared frequently after three or four doses had been administered. However, when dosage was begun at levels of 50 mg. and increases were made gradually or when the doses were widely separated, for example, by a 12-hour interval, headache occurred less frequently. In the 17

cases treated in this way headache occurred in four and in only two was it severe. In two the headache was mild and disappeared in one case without change in dosage, and in the other with slight reduction of dosage.

Moderate tachycardia with heart rates of 90 to 100 beats per minute was present in all patients in whom hypotension had been induced by 1-hydrazinophthalazine. Palpitation was complained of in five patients given this drug continuously and in two given single doses. Transient dyspnea accompanied by slow deep respirations was associated with marked reductions of blood pressure in two patients during the early phase of continuous therapy. Flushing of the face and upper extremities with injection of the conjunctivae occurred in about 25 per cent of the cases during marked hypotensive reactions. Mild flushing was present one to two hours after medication in most patients.

Dizziness and weakness occurred in four patients after single oral doses and early in the period of chronic treatment in six additional patients. All of the side effects appeared to be aggravated by exertion. Postural hypotension occurred only following acute administration and was never of sufficient severity to result in collapse (table 1). Nausea and vomiting developed in two patients during chronic administration. One patient who had no previous allergic manifestations exhibited urticaria while under treatment with 1-hydrazinophthalazine.

Therapy Using Alternating Doses of 1-Hydrazinophthalazine (C-5968) and Hexamethonium (C6)

Previous studies in this clinic[9, 10] confirmed the results of other investigators[11, 12] regarding the marked hypotensive effect of the ganglionic blocking agent, hexamethonium (C6), in patients with hypertension. Our observations indicated that the effects of oral administration of C6 were unpredicatable, apparently due to sporadic absorption. The hypotensive response following parenteral administration was considerably more uniform, but injections repeated more than two or three times per day were impractical over a period of months or years. However, with an interval of 8 or 12 hours between injections it was observed frequently that some escape occurred with elevation of blood pressure during the latter part of each injection period.

In order to combat these fluctuations of arterial pressure, other agents which could be administered orally were given midway between the doses of hexamethonium. Examples of such agents have been veratrum viride, 1-hydrazinophthalazine, the dihydrogenated alkaloids of ergot, N-benzyl-N-phenoxyisopropyl-beta-chloroethylamine (SKF 688-A), and the imidazoline compounds Regitine (C-7337) and Priscoline. The most effective of these when alternated with hexamethonium has been 1-hydrazinophthalazine.

Nine hospitalized patients who manifested a fluctuating type of blood pressure while receiving injections of hexamethonium at 12-hour intervals were given 1-hydrazinophthalazine orally midway between the doses of hexamethonium (table 2). Usually the patients were given hexamethonium at 9:00 a.m. and 9:00 p.m. and 1-hydrazinophthalazine at 3:00 a.m. and 3:00 p.m. The blood pressure was recorded in the supine position immediately before and one hour after each medication as well as at other times of day. During the control period prior to any medication (which lasted five days or longer), the average blood pressure for the entire group of patients was 210/140 and the range 160/115 to 250/165. After regulation of the dosage of hexamethonium given alone, the average blood pressure was 180/120 and the range 150/105 to 215/135. However, all of these patients exhibited low pressures for the first six hours after each injection of hexamethonium. When 1-hydrazinophthalazine was added the average blood pressure for the group was 165/105 and the range was 130/95 to 200/125. (table 2).

The doses of 1-hydrazinophthalazine varied between 50 and 150 mg. The initial dose always was 50 mg. and this was increased depending upon the hypotensive response or the development of side effects. Mild side effects occurred in only two patients and were readily controlled by slight reduction of dosage without loss of the hypotensive response. Evidence of tolerance to 1-hydrazinophthalazine appeared in five of

the cases, but was slower to develop and was not as complete as that which occurred when the doses of the drug were given alone at more frequent intervals. Further elevation of dosage of 1-hydrazinophthalazine or temporary withdrawal for a few days restored the initial hypotensive effect.

270/170, the fundi exhibited grade III hypertensive changes and there was no heart failure. There was no significant lowering of arterial pressure during the sodium amytal sedation test. The blood nonprotein nitrogen was 35 mg. per 100 cc., but the maximum urine concentration was 1.014 and the excretion of phenolsulfonephthalein was 5 per cent in 15 minutes and 40 per cent in two hours. There was

TABLE 2.—*The Effect of Hexamethonium Alone and Later of Hexamethonium Alternated with 1-Hydrazinophthalazine on the Blood Pressure of Hypertensive Patients**

Patients	Pretreatment			Hexamethonium			Hexamethonium and Hydrazinophthalazine		
	Period of Observation *days*	No. of Observations	Arterial Pressure *mm. Hg* Mean and Standard Deviation	Period of Observation *days*	No. of Observations	Arterial Pressure *mm. Hg* Mean and Standard Deviation	Period of Observation *days*	No. of Observations	Arterial Pressure *mm. Hg* Mean and Standard Deviation
J. Mc.	5	30	204 ± 20 120 ± 1	5	37	169 ± 30 111 ± 18	6	32	149 ± 23 98 ± 15
J. J.	5	32	200 ± 11 139 ± 11	8	51	152 ± 13 103 ± 12	3	15	153 ± 13 102 ± 8
G. T.	5	29	165 ± 15 139 ± 9	5	23	149 ± 14 109 ± 8	11	86	130 ± 19 94 ± 13
A. Z.	10	60	220 ± 17 140 ± 8	6	36	193 ± 15 129 ± 9	8	48	161 ± 14 117 ± 8
L. G.	7	36	250 ± 15 164 ± 9	10	52	200 ± 31 132 ± 18	10	48	195 ± 25 116 ± 9
H. B.	7	42	220 ± 13 134 ± 8	7	43	190 ± 24 121 ± 12	5	26	187 ± 16 111 ± 9
I. E.	7	36	215 ± 24 155 ± 15	10	51	194 ± 16 137 ± 11	9	43	200 ± 15 124 ± 11
J. L.	9	56	230 ± 10 135 ± 6	4	28	215 ± 13 120 ± 11	8	51	185 ± 18 105 ± 12
E. J.	6	42	205 ± 19 135 ± 9	8	50	160 ± 22 120 ± 14	7	43	150 ± 17 110 ± 10

* All patients were hospitalized throughout the various periods of observation.

The following case is worthy of special mention not only because of the success of alternating therapy, but also because the patient illustrates the development of tolerance during the use of any single agent.

L. G., a 54 year old Negro man with hypertension discovered two years previously, was admitted to the hospital complaining of dull occipital headaches of six months' duration. Recently there had been nocturia and vomiting. The blood pressure was

pyuria and bacilluria, and the intravenous pyelogram revealed changes consistent with chronic pyelonephritis. Several courses of antibiotics, including Chloromycetin, Terramycin and streptomycin, were given to combat the urinary infection but all were uniformly ineffective in producing sterilization of the urine.

While under treatment for five days with a diet containing 200 mg. of sodium daily, the blood pressure, which was recorded six times per day, averaged 250/165 (range 230/160 to 270/170). Anaten-

sol* was administered orally for five weeks in doses of 0.5 to 1.5 mg. four times per day. The average arterial pressure during this time was 190/130 (range 150/110 to 215/160). However, during the last two weeks the blood pressure gradually rose to an average level of 230/155 (fig. 2).

1-Hydrazinophthalazine (C-5968) was administered orally in doses of 100 mg. every four hours for one day with slight reduction of average blood pressure from 230/150 to 200/140, but headache occurred and this medication was discontinued. For the next four weeks hexamethonium (C6), 40 mg. of the ion every six hours, was given with significant reduction of arterial pressure to an average level of 180/130 during the first week, but then the blood pressure gradually rose despite increase of the doses of hexamethonium to 80 mg.

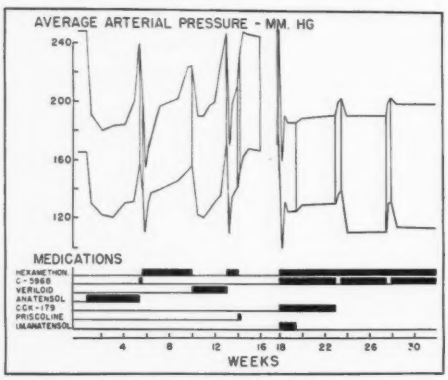

FIG. 2. Chart of the arterial pressure and types of drug therapy used in patient L. G., a 54 year old Negro man, with chronic pyelonephritis and malignant hypertension. Tolerance occurred following each agent used separately but was avoided when 1-hydrazinophthalazine and hexamethonium were used alternately. See text for further details.

Veriloid† was then administered alone for the next three weeks. The total daily dosages ranged from 21 to 24 mg. which were sufficient to cause occasional nausea and vomiting. During this period the average arterial pressure was 200/130. At the end of three weeks tolerance to Veriloid appeared and hexamethonium alone was resumed in doses of 40 to 50 mg. every six hours for the next week. Initially there was a significant hypotensive response with reductions of blood pressure to a low of 150/90 with an average of 190/120. However by the third day of this therapy tolerance again developed with the average blood pressure rising to 200/135. A brief trial of Priscoline was without effect (fig. 2).

During 14 weeks of hospitalization, while under intensive treatment with many hypotensive agents, there had been no sustained reduction of blood pressure. Following hexamethonium, Anatensol or Veriloid there was a temporary reduction of arterial pressure, but none of the drugs produced sustained responses due apparently to the gradual development of tolerance.

All medication was then discontinued for the next 15 days during which period the average blood pressure was 240/155 (range 230/150 to 260/170). Frequent and severe headaches soon returned. However, since the patient did not respond or quickly developed tolerance to all medications he was discharged on no specific therapy.

Two weeks later the patient was readmitted acutely and severely ill. During the short time that he had been home all symptoms had become rapidly and progressively worse. The blood pressure was 230/170. The fundi now exhibited papilledema of three diopters. There was mental confusion, severe headache, vomiting and pulmonary congestion with dyspnea and orthopnea and the nonprotein nitrogen was 50 mg. per 100 cc.

Because of the previous experience demonstrating an apparent development of resistance to all hypotensive agents when used continuously it was decided to use various drugs in rotation, so that no single agent was used twice in succession, in an attempt to forestall the development of tolerance. The doses of the drugs used were 25 to 50 mg. of hexamethonium ion intramuscularly, 25 to 150 mg. of 1-hydrazinophthalazine (C-5968) orally, 0.3 mg. of mixed dihydrogenated alkaloids of ergot (CCK-179)* intramuscularly, 0.25 to 0.50 mg. of Anatensol intramuscularly and 50 mg. of Priscoline orally. These were given at six-hour intervals in various rotations so that no single agent was administered more frequently than once every 24 hours. Sodium restriction to 200 mg. daily was continued.

Initially dosages of these substances (C6, C-5968, Anatensol and CCK-179) were administered in that order at six-hour intervals. There was a pronounced fall of arterial pressure from the admission level of 230/170 to an average level of 175/120, accompanied by marked clinical improvement. After several days it was noted that the greatest reduction of arterial pressure occurred after injection of hexamethonium, whereas the poorest responses were observed to follow the ergot preparation and Anatensol. Hence, the latter agent was replaced by a second injection of hexamethonium. Over the five-week period that

* Extract of veratrum viride obtained from the Squibb Institute for Medical Research, New Brunswick, N. J.

† Extract of veratrum viride obtained from the Riker Laboratories, Los Angeles, Calif.

* Mixed dihydrogenated alkaloids of ergot obtained from Sandoz Pharmaceuticals, New York, N. Y.

these two treatment programs were used the blood pressure averaged 180/125 and ranged from 130/90 to 210/130. When hexamethonium was given alone at 12-hour intervals for one week, the blood pressure averaged 200/135 and ranged from 150/100 to 240/145. Then 50 to 100 mg. of 1-hydrazinophthalazine orally and 50 mg. of hexamethonium were given alternately at six-hour intervals with further reduction of average arterial pressure to 185/115 (range 140/105 to 220/140). This level was maintained for four weeks and again, while administering hexamethonium alone at 12-hour intervals, the blood pressure became elevated to an average of 205/130 (range 170/110 to 235/145). When 1-hydrazinophthalazine was resumed midway between doses of hexamethonium there was again a fall in average arterial pressure with diminished fluctuations.

This intensive treatment program utilizing hypotensive agents alternately has now been continued for nearly four months with a sustained satisfactory response even after discharge from the hospital. Soon after institution of treatment there had been rapid improvement in all symptoms and in pulmonary congestion and by the end of two months there was complete regression of the papilledema.

Discussion

Although single oral doses of 1-hydrazinophthalazine frequently were followed by a significant hypotensive response the usual result of continuous therapy was the progressive development of tolerance as observed previously by Grimson and co-workers.[13] Increasing doses of 1-hydrazinophthalazine restored the hypotensive response at least partially but over a period of several weeks tolerance was marked even with amounts three to four times as great as those used initially.

This resistance to the hypotensive effect of the drug was not lasting, however, and sensitivity to the initial small doses of 1-hydrazinophthalazine could be restored by omitting the medication for one week. In addition it was apparent that the greater the interval between doses the less marked was the degree and the more delayed the development of such resistance.

Over long periods in the treatment of hypertension, tolerance in varying degree has developed following almost all hypotensive agents, including sodium nitrite,[14] veratrum viride,[15] the dihydrogenated alkaloids of ergot,[16] Priscoline and Regitine,[17] SKF-688A, and hexamethonium.[10] Because of this phenomenon we have leaned increasingly toward the concept that effective long-term chemotherapy of essential hypertension using presently available agents must utilize these drugs alternately. This rotation might prevent or at least allay the development of a significant degree of tolerance. The most effective of these combinations in our experience has been 1-hydrazinophthalazine alternated with hexamethonium. In many of the cases receiving hexamethonium alone twice per day (in the morning and at bedtime) the greatest elevation of blood pressure occurred in the evening whereas the effect of the dose taken at bedtime frequently carried over until next morning. In these cases 1-hydrazinophthalazine was given only once per day, in the midafternoon, and thus the necessity for awakening to take the drug at 3:00 a.m. was obviated.

In many instances tolerance to hexamethonium can be overcome by progressive elevation of dosage. Hence, it is possible in some cases to maintain a sustained hypotensive effect by using large oral doses of hexamethonium frequently administered. But such complete and lasting autonomic blockade also induces in varying degree gastrointestinal atony, paralysis of visual accommodation, disabling postural hypotension, lethargy and impaired cerebration, impotence in the male, shivering in a cool environment due to failure of cutaneous vasoconstriction, loss of bladder tone and cessation of salivary secretion. Although some of these effects can be partially controlled with the use of parasympathomimetic agents such as Urecholine,[9] many of these patients are unable to carry on a normal existence. Thus, although a sustained hypotension is attainable in some instances by oral administration of large doses of hexamethonium, such intensive treatment may on occasion produce fatalities[19] and frequently induces disabling side effects. Therefore, in long-term therapy it has seemed more desirable and considerably safer to produce intermittent rather than continuous ganglionic blockade supplementing and prolonging the hypotensive effect with 1-hydrazinophthalazine.

In addition to its synergistic effect when used with hexamethonium, 1-hydrazinophthalazine

also appeared to have an additive effect when given with veratrum viride. Three patients in whom the control of blood pressure was unsatisfactory using veriloid alone obtained an improved hypotensive response when 1-hydrazinophthalazine was added once or twice daily.[18]

The side effects produced by 1-hydrazinophthalazine appeared to be related to the dosage level and also to the frequency of administration. Doses of this drug (C-5968) which produced a profound hypotension also were most likely to be associated with side effects, particularly headache and palpitation. If treatment was initiated using doses of 25 to 50 mg. and increased over a period of a week to the most effective range these undesirable reactions were minimized. They also were seen much less frequently when the dosage interval was no less than 12 hours and especially when treatment was alternated with hexamethonium.

In addition to increasing renal blood flow, 1-hydrazinophthalazine appears to have other desirable attributes, including effectiveness by the oral route of administration, absence of serious toxicity and ability to lower diastolic as well as systolic blood pressure. As to the ultimate place of 1-hydrazinophthalazine in the therapy of essential hypertension, it is suggested by these studies that the drug probably is of greatest value when used in conjunction with other agents, particularly when alternated with hexamethonium.

Summary and Conclusions

1-Hydrazinophthalazine (C-5968) was administered to a series of hypertensive patients with the following results:

1. Single oral doses of 50 to 150 mg. resulted in a significant reduction of blood pressure, especially of diastolic pressure, in 12 of 16 patients tested. Moderate postural hypotension occurred in 15 of these cases.

2. Attempts to maintain a significant reduction of arterial pressure by frequent administration of the drug usually led to the rapid development of tolerance. The latter could be partially overcome by (a) increase in dosage, (b) prolonging the interval between doses, and (c) omitting the medication entirely for a period of one week. Persistent reductions of arterial pressure over prolonged periods were rarely attained with 1-hydrazinophthalazine alone.

3. Side effects, observed inconstantly included severe headache, tachycardia with palpitation, flushing of the skin, dizziness and weakness, and rarely, dyspnea and nausea and vomiting. Such reactions could be minimized by gradual increases in and wide spacing between dosages of 1-hydrazinophthalazine.

4. 1-Hydrazinophthalazine (C-5968) was most effective when used alternately with other hypotensive agents, particularly with hexamethonium (C6). Such intermittency of dosage appeared to minimize the development both of side effects and of tolerance and resulted in a greater and more sustained reduction of blood pressure than when either agent was used alone.

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Cation Exchange Resin in the Treatment of Congestive Heart Failure

II. Clinical Effectiveness and Chemical Complications during Prolonged Periods of Use

By W. C. KLINGENSMITH, JR., M.D., AND J. R. ELKINTON, M.D.

Thirty-four edematous cardiac patients who were being treated with cation exchange resin were studied for its long term effectiveness and for clinical and chemical complications. In 23 of 27 patients the resin was effective in terms of mobilizing edema fluid previously refractory to other forms of treatment, of partial or complete substitution for mercurial diuretics, and of permitting a slight increase in the salt content of the diet. Gastrointestinal intolerance was the chief clinical complication but prevented therapy in only five patients. Chemical complications of sodium depletion, potassium depletion or excess, and severe chloride acidosis were not seen.

IN THE preceding paper[1] data were presented concerning some of the electrolyte exchanges which result from the use of cation exchange resin in edematous cardiac patients. It was shown that resin will increase the fecal excretion of sodium and potassium, and that in certain patients, previously refractory to treatment with mercurial diuretics, the addition of resin therapy appeared to cause the elimination of their edema. This loss of edema resulted from increased urinary as well as fecal excretion of sodium. These studies, however, gave no information concerning the clinical effectiveness of the administration of resin to such patients over a prolonged period of time, or of the possible complications of such therapy during its long-term use. It is the purpose of this paper to supply such information.

EXPERIMENTAL MATERIAL

Observations were made on a total of 34 patients with peripheral edema due to congestive heart failure. The etiologies of the heart disease in these patients were as follows: chronic rheumatic disease, 15; hypertension, 10; arteriosclerosis, 7; and syphilis, 2. In 27 of these patients resin therapy was continued long enough to evaluate its long-term effectiveness, the maximum period of treatment being 62 weeks and the average period being 26.4 weeks. The remaining seven patients of the total series are included in order to give a fair picture of patient tolerance to the preparation.

The 27 patients in whom long-term therapy with resin was evaluated are placed in three classifications for purposes of analysis. Class I is made up of 16 patients in whom congestive heart failure persisted despite intensive treatment by standard methods. These methods included digitalization, sodium deprivation (below 500 mg. daily in most cases), frequent administration of mercurial diuretics, and restricted activity including a period of bed rest in the hospital during the initial period of study. Class II consisted of five patients who had been maintained in an edema-free state on an 800 to 2000 mg. sodium diet by the administration of digitalis and mercurial diuretics. Class III included six edematous patients who were on digitalis but who were unable to take mercurial diuretics due to sensitivity to the drug. Besides the 27 patients included in these three classes, seven patients are tabulated as class IV who were unable to tolerate the resin over a prolonged period or who were not followed closely enough to permit adequate evaluation.

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The authors are indebted to Dr. Charles C. Wolferth for counsel and for making his private patients available for this study. Dr. C. J. Martin also assisted this study by following the first group of patients.

J. R. E. is an Established Investigator of the American Heart Association.

Method of Study

Cation exchange resin was administered to these patients as a mixture of ammonium and potassium forms in a 3:1 ratio.* In all but a few patients the daily dosage was 45 Gm. divided into three equal parts. The resin was suspended in a liquid vehicle of the patient's choice and was taken just before, during, or just after meals as preferred. The potential hazard of calcium depletion was met by adding calcium in the form of three glasses of whole or dialyzed milk per day, or 3 Gm. of calcium gluconate (in one patient who was unable to tolerate milk). A mixed vitamin preparation was added because of the possibility of vitamin depletion.

Except for occasional periods of hospitalization, these patients were studied in the outpatient clinic. Positive results are therefore more significant than negative results although every effort was made to ascertain whether or not the patient was following the prescribed regimen. The clinical effectiveness of the resin therapy was assessed as *effective*, *equivocal*, or *ineffective* in a qualitative manner as follows. Resin therapy in patients in class I (edematous despite all other therapy) was judged to be effective if its addition to the other therapeutic agents resulted in a diminution of the edema. In class II (patients maintained in an edema-free state by digitalis and mercurials) the resin was considered to be effective if it was successfully substituted in part or in whole for the mercurial diuretics. In both classes I and II an increase in the salt content of the diet without concomitant fluid retention was taken into account in judging effectiveness of the resin. In class III (patients with edema and with sensitivity to mercurials) the resin was judged to be effective if the edema diminished.

Clinical complications were watched for and are recorded. Chemical complications were assessed primarily in terms of changes in concentrations in serum and whole blood of electrolytes and urea nitrogen, respectively.† In the early stages of the study, serum concentration of sodium, potassium, chloride, and total carbon dioxide content were determined every one or two weeks. In the later stages these determinations were made at somewhat longer intervals. The serum calcium concentration was determined periodically in some of the patients.

* The resin mixture given to these patients was a carboxylic resin in the ammonium and potassium cycle in the ratio of 3:1, each 45 Gm. containing approximately 60 mEq. of potassium. It is marketed under the trade name Resodec, and was supplied for this study through the courtesy of Smith, Kline, and French Company, of Philadelphia.

† The chemical methods used are the same as in the preceding paper.[1]

Results

The results are presented in tables 1 and 2 and in figures 1 to 3.

Clinical Effectiveness

The effectiveness of the resin therapy in the 27 patients in classes I to III is summarized in table 1. In *class I* the treatment was considered effective in 13 patients, equivocal in two, and probably ineffective in one. In the effective group the introduction of resin into the therapeutic regimen was followed by a loss of edema, and later by reduction in mercurial dosage. In most of the cases it was also possible to discontinue the severe dietary restriction of sodium and to allow the use of a more easily prepared "low salt" diet containing an estimated 800 to 1600 mg. of sodium per day. The clinical course of one of the patients typical of this group is shown in figure 1. Of the patients rated as showing an equivocal response to resin, one had an encouraging early response to

Table 1.—*Clinical Effectiveness and Duration of Resin Therapy*

	Class			Total
	I	II	III	
Effectiveness				
Effective	13	5	5	23
Equivocal	2		1	3
Ineffective	1			1
Total	16	5	6	27
Duration of Therapy				
Minimum, weeks	2	15	5	2
Maximum, weeks	59	62	36	62
Average, weeks	20.5	43.2	28.2	26.4

Table 2.—*Clinical Complications**

Constipation	7
Hemorrhoidal bleeding	2
Abdominal cramps and/or diarrhea	6
Anorexia or nausea without vomiting	9
Vomiting	2
Muscle cramps	2

* Twenty of the 34 patients in classes I to IV had these complaints. Resin therapy was interfered with in 11, and permanently discontinued in 5 patients.

the resin but was forced to discontinue it because of gastrointestinal intolerance; the other improved symptomatically but required the same amount of mercurial diuretic and sodium restriction as before resin therapy. The one patient classed as ineffective developed gastrointestinal intolerance, stopped the resin, and died shortly afterward of progressive cardiac failure.

In *class II* (patients maintained in a compensated state by digitalis and mercurial diuretics) the resin was considered effective in all five patients in terms of completely or partially replacing the mercurials. Three of these patients have been followed for more than a year on resin and have required only infrequent doses of mercurial diuretics. In the two patients followed for somewhat shorter periods the resin appeared to be a completely adequate substitute for the mercurials. In one of the patients in this class repeated attempts were made to increase the dietary intake of salt from approximately 800 mg. of sodium to approximately 2400 mg. of sodium per day; each time the accumulation of edema fluid promptly occurred.

In *class III* (edematous patients who were sensitive to mercurials) the resin was effective in five patients and equivocal in one patient. The results were dramatic in one anasarcous patient who lost 21 Kg. of weight in one month. The case classified as equivocal was the patient in whom therapy was finally discontinued because of gastrointestinal intolerance and who was suspected of failing to take the recommended dosage of resin.

Of the 27 patients in classes I, II and III treated for an average period of 26.4 weeks, the resin appeared to be effective as an adjunct to, or partial substitute for, other therapy in 23 patients.

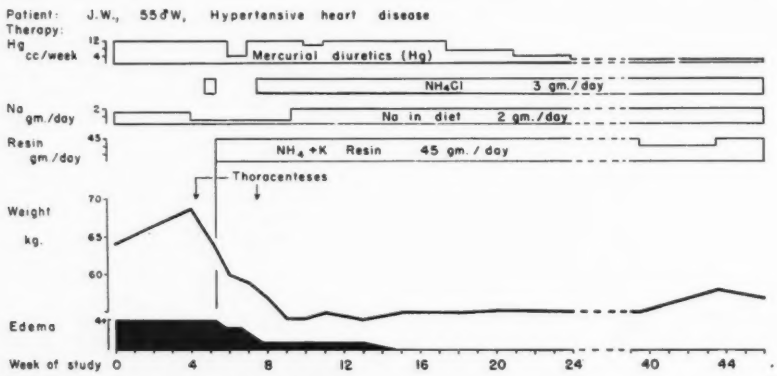

FIG. 1. An example of the prolonged use of cation exchange resin as an adjunct to the treatment of the edema of congestive heart failure. The elimination of the edema during the period of weeks 4 to 9 would appear to be the result of a number of factors including a reduction in dietary sodium, the performance of thoracenteses, and the institution of ammonium chloride, as well as of resin therapy. On these last two medications, however, the patient was maintained in an edema-free state up to the forty-sixth week of study with a 2 Gm. sodium diet and with a marked reduction in the weekly dosage of mercurial diuretics.

Clinical Complications

The clinical complications in the 34 patients in classes I through IV are summarized in table 2.

Gastrointestinal intolerance was the principal type of complication. Increase in the size and firmness of the stool was noted by almost all the patients. Constipation causing a complaint on the part of the patient was observed in only seven cases. Hemorrhoidal bleeding occurred in two patients and was of sufficient severity in one of these to require temporary discontinuation of the therapy. Abdominal cramps with or without diarrhea were noted

in six patients and were sufficiently severe to necessitate discontinuation of therapy permanently in two, and temporarily in three patients. Anorexia or nausea without vomiting were observed in nine patients and in two of these were sufficiently severe to stop the therapy. Two patients vomited the resin when initially administered and so could not be treated.

Muscle cramps occurred occasionally in two patients; one of these had had more severe cramps following mercurial diuretics.

incidence of such complications are presented as follows.

Sodium depletion with concomitant peripheral vascular collapse and renal failure was looked for as a possible result of overtreatment with resin. Since this condition in cardiac patients, commonly called the "low salt syndrome," is usually accompanied by hyponatremia,[3, 4] the cardinal chemical index was the serum concentration of sodium. In figure 2 the distribution of 101 determinations of this value obtained during resin therapy in 23 patients is

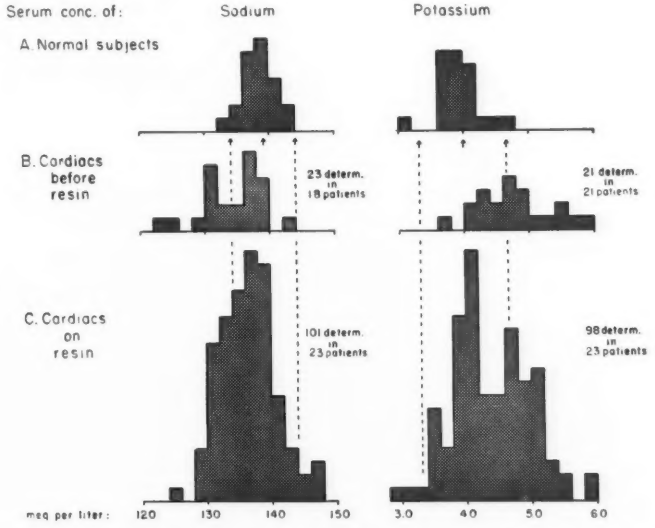

FIG. 2. Distribution curves of the serum concentrations of sodium and potassium in edematous cardiacs before and during resin therapy. The distribution of levels in 21 normal subjects is shown at the top of the figure; the dotted lines represent 2 standard deviations from the mean of the normal group. The mean concentration of sodium is higher and that of potassium lower in the cardiacs during resin therapy than before such therapy.

Thus, of the total group of 34 patients, 20 displayed one or more undesirable effects of resin therapy. Such therapy was interfered with in 11, and permanently discontinued in five patients.

Chemical Complications

From the observations reported in the preceding paper and by other investigators as well, certain untoward biochemical effects might be anticipated from the prolonged use of cation exchange resins.[2] Data bearing on the compared with that of 23 determinations in 18 of the same patients before resin therapy as well as with the distribution of such determinations in 21 normal subjects. The mean level of serum sodium before resin therapy was clearly lower than that of the normal group, which is in agreement with the observation made in a previous series of edematous cardiac patients receiving mercurial diuretics.[5] On resin therapy, however, the mean serum level of sodium was *higher*, not lower, than before therapy, and only four values were 130 mEq.

per liter or below. The small proportion of determinations in this range, which is associated with the "low-salt syndrome," the virtual absence of severe azotemia (see below), and the failure to observe clinical signs and symptoms of peripheral vascular collapse[4, 6] are strong evidence that sodium depletion was not a serious complication in this series of patients.

Potassium deficit and excess are possible complications in view of the known capacity of the ammonium cycle resin to remove potassium and because of the addition of the potassium form of resin to patients with potential renal failure. These two abnormalities in total body potassium are usually mirrored in the serum level of the ion. In figure 2 the distribution of 98 determinations of this value in 23 of the patients during resin therapy is compared with that of 21 determinations in the same patients before resin therapy and with the distribution in 21 normal subjects. On resin the mean value for the whole group of determinations was lower than before therapy; only three values were below 3.5 mEq. per liter and none were above 6.0 mEq. per liter. Hypo- or hyperkalemia were not, therefore, frequent complications of resin therapy in this group of patients, and insofar as the serum level reflects the cellular stores of the ion, deficit or excess of total body potassium did not occur to a serious extent. There were no clinical signs of changes in potassium concentration.

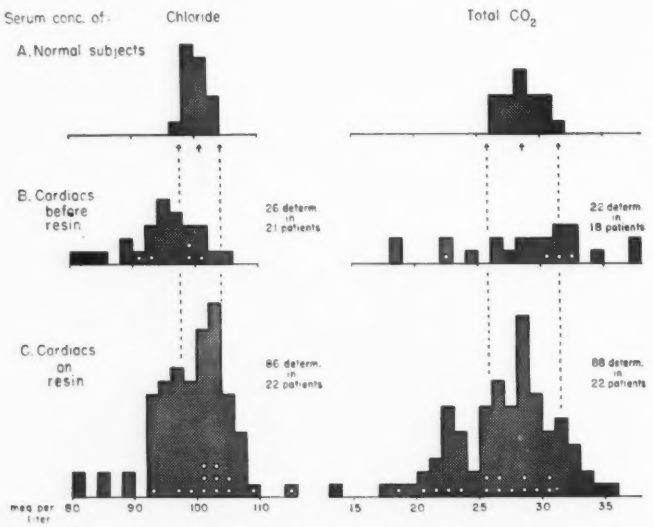

FIG. 3. Distribution curves of the serum concentrations of chloride and total carbon dioxide content in edematous cardiacs before and during resin therapy. The distribution of levels in 18 normal subjects is shown at the top of the figure; the dotted lines represent 2 standard deviations from the mean of the normal group. The open circles indicate those values determined during the oral administration of ammonium chloride. The mean concentration of chloride was somewhat higher, and that of carbon dioxide slightly lower, during resin therapy than before resin therapy, but extreme changes were not observed. Ammonium chloride administration was not associated with the highest chloride or the lowest carbon dioxide values in either group.

Chloride acidosis has been reported as a serious complication of the administration of ammonium or hydrogen cycle exchange resins. In figure 3 are presented the distributions of 86 determinations of the serum concentration of chloride and 88 determinations of the total content in serum of carbon dioxide in 22 patients on resin therapy. These distribution curves are compared with the distribution of such values in most of the patients before resin therapy, as well as with those of a group

of normal subjects. In the edematous cardiacs before resin therapy, the serum chloride concentrations tended to be low and the total carbon dioxide contents both low, normal, and high (as previously reported[5]). On resin the mean chloride value rose and that of the carbon dioxide perhaps fell slightly. The concomitant administration of ammonium chloride was not strictly associated with the highest chloride and lowest carbon dioxide levels. Since only one chloride value was above 110 mEq. per liter and one carbon dioxide value below 15 mM. per liter, chloride acidosis in terms of these measurements was not a serious or frequent complication. pH values were not determined. In none of this group was there any clinical evidence of acidosis.

Renal failure, assessed in terms of marked azotemia, was present in only one patient in this series. This patient had intrinsic renal disease of a severe degree (blood urea nitrogen of 50 mg. per 100 ml.) before resin therapy was instituted; on resin the carbon dioxide content fell to 13.5 mM. per liter (fig. 3). Following discontinuation of his resin therapy, the acidosis responded to treatment with sodium bicarbonate but the azotemia progressed until death two weeks later. In three other patients, one of whom had a normal control value, the blood urea nitrogen increased slightly. In six of eight patients with a mild degree of azotemia before resin, the azotemia decreased during therapy. Thus, despite the report of the production of urinary casts by resin,[7] renal failure was not a direct complication of resin therapy in our series.

Calcium depletion was a possible complication since ammonium cycle resin is known to take up this divalent cation preferentially in vitro. Serum concentrations of calcium were determined 30 times in 12 patients during therapy. No values were found below 9.0 mg. per 100 ml. Although the maintenance of a normal serum level does not rule out a slow depletion of the calcium stores of the body, it does suggest that such did not occur to a serious extent. There was no evidence of tetany. X-ray studies for decalcification were not made.

Discussion

The results obtained in this study indicate clearly that the administration of cation exchange resin is a useful adjunct in the treatment of patients with congestive heart failure. It appears to be helpful in the control of such edema over prolonged periods of time as well as in the treatment of edema which has become refractory to other forms of therapy.[1] The term "adjunct" is used advisedly, since the use of resin did not remove the necessity of employing other accepted methods of treatment. Digitalis preparations were administered to all of the patients in the usual doses, and physical activity was restricted. The resin, therefore, modified the previous therapeutic regimen in two ways: (1) the partial or complete elimination of mercurial diuretics, and (2) an increase in the salt content of the diet.

Mercurial diuretics have been such an extremely useful tool in the treatment of cardiac edema that they are unlikely to be supplanted by exchange resins. However, mercurial therapy has its limitations. Some patients are sensitive to these drugs. Some patients become refractory to the diuretic action of mercurials, and in some a "low salt syndrome," characterized by peripheral vascular collapse and progressive renal failure, may ensue.[4] For these reasons cation exchange resin may be a useful adjunct in potentiating the action of mercury in refractory patients,[1] in reducing the number of doses, or in eliminating entirely the necessity for the drug.

Resin therapy in edematous patients was originally introduced with the thought that it would obviate the necessity for an unpalatable salt-free diet. The evidence of other investigators, as well as of our own, supports this concept within certain limits. Resin appears to take up primarily exogenous or dietary sodium, but the degree to which it does so is limited. Thus, in the group of patients reported here it was usually possible during resin therapy to change from a "salt-free" diet (less than 500 mg. of sodium) to a "low-salt" diet (800 to 1600 mg. of sodium). This latter diet contains 35 to 70 mEq. of sodium, an amount which somewhat exceeds the daily fecal sodium excre-

tion observed in patients on ammonium plus potassium resin (Resodec) but which lies within the range of 40 to 90 mEq. of sodium in stools excreted by the usual route by patients receiving ammonium cycle resin.[1] When the dietary intake of sodium was increased above this range (2000 to 2400 mg. of sodium or 85 to 100 mEq. of sodium) edema fluid began to reaccumulate. Resin, therefore, does not give a *carte blanche* for adding salt to the diet. However, the difficulty in preparation of a 500 mg. sodium diet as compared to an 800 to 1600 mg. sodium diet is such that there is a very real advantage in the use of resin on this score.

Against these advantages certain disadvantages must be weighed. One of these is the present high cost of the drug. However, this disadvantage soon may be minimized as a result of improved methods of production and commercial competition. More serious is the problem of gastrointestinal intolerance, the incidence of which was high in this group of patients. Anorexia and nausea may be controlled in the majority of instances by a trial and error attempt at finding the most suitable liquid in which to suspend the resin for administration. In addition, reactions of this type frequently were minimized by permitting the patient to take the resin suspension in small sips during meals, and by guarding against settling of the resin towards the bottom of the suspension. Constipation was a common complication in the series but was usually controlled by the use of mineral oil and a mild laxative. Abdominal cramps and diarrhea were more difficult to treat and sometimes necessitated a period of rest from the resin administration. These difficulties encountered in resin therapy indicate the need for improvement of the agent along lines of increased palatability and increased effectiveness in cation exchange permitting the use of smaller doses of resin. Nevertheless, most of our patients found that the advantages of the resin outweighed the difficulties and were willing to continue the therapy.

The data reported on this series of patients are reassuring in regard to the potential biochemical hazards of the use of cation exchange resins over a prolonged period of time. The occurrence of sodium depletion with peripheral vascular collapse and renal failure has been reported to occur following the use of such resins.[8,9] In our series these complications were not observed; this inclines us to the belief that, properly guarded against, such complications are not a common danger. Potassium depletion was reported early in the experimental use of ammonium cycle resin[10] and was the reason for adding potassium cycle resin to the ammonium form for ordinary therapeutic use. While carboxylic resin combined in these two cycles is less effective in removing sodium than the ammonium cycle resin alone,[1] it does appear not only to have been clinically effective in controlling edema but also to have prevented the development of a serious degree of potassium depletion during prolonged use. On the other hand, another complication was anticipated from the addition of the potassium cycle resin to the regimen, namely, potassium retention and intoxication. Such intoxication is usually the result of renal insufficiency[11] and might be anticipated in a group of edematous cardiacs whose renal function is generally less than optimum. Nevertheless, in our group of patients this complication was not encountered, its absence probably being due to the usual avoidance of patients with any marked degree of renal failure.

The production of a severe degree of chloride acidosis has been considered to be one of the principal hazards of the use of cation exchange resins,[2, 12, 13] and has been the reason for the combination of an anion exchanger with the cation exchange resin.[14] Such a complication does occur readily in patients with a severe degree of renal disease,[15] but did not occur in our group of edematous cardiac patients. In wisely selected patients, therefore, fear of such a complication should not deter the physician from the use of ammonium or hydrogen plus potassium cycle resins. The employment of a combination of anion and cation exchange resins may well have a place in treating edematous patients with advanced renal failure, but such combinations may be less effective in treating edematous cardiac patients without renal failure. The presence of a mild acidosis

has long been known to predispose toward a diuresis, and the data in the preceding paper suggest that it may be one factor in the potentiation by resin of the renal effect of mercurial diuretics.[1]

Evidence of calcium depletion was not found in this series although the resin has been shown to have a preferential affinity for divalent cations in vitro. In vivo balance studies have indicated that large amounts of calcium are not lost with ammonium and hydrogen cycle resins,[16] presumably because of the low concentration of dissolved calcium in comparison with that of sodium in gastrointestinal fluids. The data on this point in this paper, however, are indirect since serum levels may not mirror a calcium depletion and since the patients were maintained on a fairly high calcium intake.

The possibility of the production of other deficiencies, such as magnesium, iron, thiamine, and riboflavin, has been suggested,[12, 16] but we saw no evidence of this. However, until we are sure they do not occur, supplementary minerals and vitamins should be added during prolonged resin therapy.

Cation exchange resins have given the physician a new tool with which to remove from the body certain constituents which are undesirable. The observations reported in this paper indicate to the authors that such resins have a useful role in the therapy of chronic congestive heart failure but that they must be used with care and with due consideration of their limitations. Like any other manipulation of a biochemical and physiologic disturbance due to a disease state, resin therapy of the edematous cardiac requires careful thought concerning the individual patient. But used in this way, and not as an infallible panacea, it should develop into a dependable item of the physician's armamentarium.

Summary and Conclusions

Cation exchange resin, in the ammonium plus potassium cycle, was administered to 34 patients with edema due to chronic congestive heart failure. In 27 of these patients the treatment was sufficiently documented to permit assessment of its long-term effectiveness, the average length of therapy being 26.4 weeks and the maximum being 62 weeks. The results were as follows:

1. In terms of elimination of edema in previously refractory patients or of prevention of reaccumulation of edema during a decrease in mercurial diuretic and salt restriction therapy, the resin was effective in 23 of the 27 patients.

2. Gastrointestinal complications occurred in 20 of the 34 patients but required the discontinuance of the resin in only five patients.

3. No evidence of the following chemical complications were observed: sodium depletion, potassium depletion or intoxication, severe chloride acidosis or calcium depletion.

It is concluded that, with the careful selection of patients, cation exchange resin in this form is a useful and safe adjunct to the treatment of chronic congestive failure over prolonged periods of time.

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The Use of Crystalline Visammin in the Treatment of Angina Pectoris

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The high incidence of unpleasant side effects following the use of crude preparations of khellin in the treatment of angina pectoris has limited its clinical use. It was felt that if this vasodilator drug were prepared free of resins, chromones and other plant impurities, it might then be used more extensively in the treatment of coronary insufficiency. Currently, a crystalline preparation of high purity has become available. A series of patients with angina pectoris were studied using this preparation. A Starr ballistocardiograph was interjected into our study in an attempt to obtain objective evidence of any effect this drug might have on the mechanical action of the heart.

FROM ANCIENT times the people of Arabia and the Eastern Mediterranean countries have used extracts, tinctures and other preparations made from the seeds of *Ammi visnaga* (Arabic khella) for the treatment of renal colic and ureteral spasms due to renal calculi. Several crystalline substances were isolated early from the seeds of this plant. The more important of these were khellin (2-methyl - 5,8 - dimethoxyfuranochromone), visnagin (2 - methyl - 5 - methoxyfuranochromone), and khellol-glycoside, which is an oxyglycoside of visnagin.

Khellin, also known as visammin, was first prepared in an impure form by Mustapha in 1879.[1] In 1931 Samaan[2] reported on the pharmacologic action of this drug. In his experiments he utilized tinctures and extracts of the seeds as well as a crystallized material with a melting point of 153 C., which he felt was essentially pure khellin. Samaan concluded that these preparations not only relaxed all smooth muscle by direct action on the muscle fibers but also possessed a mild diuretic effect. His later studies led him to conclude that the glycoside portion of this preparation contained the active principle. In 1945 Anrep and his group[3–5] confirmed the findings of Samaan. They showed, however, that khellin and visnagin were the active principles of the drug while the glycoside portion was inactive as a smooth muscle relaxant. Anrep also demonstrated that crystalline khellin had a pronounced effect in increasing coronary blood flow and that the drug had a more prolonged therapeutic effect when compared with other coronary vasodilating drugs. Gilbert and Nalefski[6] confirmed these findings. Anrep completed his studies by treating 250 patients with angina pectoris and reported improvement in 225 cases and no improvement in 25. He noted that the drug produced only a few side effects and was not toxic with prolonged administration. He also observed that it did not affect the bleeding or coagulation time.

Following the appearance of these reports in the literature, various clinical investigations were instituted in this country. Armbrust and Levine[7] treated 53 patients with classic histories of angina pectoris with a preparation stated to contain 75 per cent khellin and 25 per cent visnagin. They concluded that 60 per cent of their patients showed improvement since they required fewer nitroglycerin tablets, had fewer and milder attacks of pain, and could walk greater distances. They reported that nausea, anorexia and dizziness occurred in about 60 per cent of the patients treated. They concluded that khellin was of value in the treatment of angina pectoris, but its usefulness was limited by the undesirable side effects encountered. In a controlled study, Osher and Katz[8] found that khellin therapy produced subjective and objective improvement in 16 of 19 patients with angina pectoris. They used the same preparation that the previ-

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ous investigators did and reported nausea, vomiting, anorexia, insomnia and vertigo as side reactions. In the same year Dewar and Grimson[9] reported a comparative study of the effects of khellin and glyceryl trinitrate on 12 patients. In the dosages studied, they found khellin to be less potent but longer acting than glyceryl trinitrate. They stated that khellin given in effective doses did not cause any unpleasant side effects and did relieve angina in one patient who was intolerant of both glyceryl trinitrate and theophylline ethylene diamine. Rosenman and co-workers[10] reported their findings using Eskel, a mixture of *Ammi visnaga* principles. From their carefully controlled experiments they concluded that visammin (khellin) was a drug with definite therapeutic effects in angina pectoris, chronic cor pulmonale, and possibly in acute bronchial asthma. They found toxic reactions in 16 cases of the total 30 studied. Greiner and co-workers[11] treated 39 patients with coronary artery disease and angina of effort with Eskel. Their method for evaluating this drug led them to conclude that the results on these 39 patients showed khellin to have no greater effect than lactose in the control of pain in the angina of effort. In their study, 35 of the 39 patients treated reported unpleasant symptoms at one time or another which were ascribed to the medication.

Our personal experiences during the past year with the crude form of the drug showed a very high incidence of side reactions similar to those reported by others. With a few exceptions, we found that 2 tablets per day of the impure preparation which contained a total equivalent of 80 mg. of khellin would produce nausea and vomiting. Frequently, patients could not tolerate even 1 tablet per day. Only rarely could a patient with angina pectoris tolerate 3 tablets per day for intervals as long as one week.

In view of the favorable laboratory reports and the beneficial clinical results usually reported in those instances where the patient could tolerate this drug, we felt that its active principles should be investigated further. We had the distinct impression that if the side effects could be eliminated, a potent medicament would be at our disposal for the treatment of coronary insufficiency.

Currently, a crystalline khellin* of 97.0 to 99.8 per cent purity having a melting point of 151 to 154 C. has become available. The physical appearance of this material is quite unlike that of the crude preparations used to date. It was felt that possibly the side effects experienced with the crude preparations would be minimized with the crystalline khellin in the absence of other plant impurities, resins and chromones. With this in mind, a series of patients were studied using the crystalline *Ammi visnaga* preparation.

Method

This investigation was conducted on 21 patients with longstanding, proved coronary artery disease, who were obtained from the Out-Patient Departments of the Florsheim Cardiac Clinic and St. Luke's Hospital. In a few instances, the patients were made available for study by private physicians during hospitalization. The diagnosis of angina pectoris was based on a past history of precordial and substernal pain on effort, emotion or following the ingestion of large quantities of food. All patients obtained relief from their symptoms after rest or following glyceryl trinitrate therapy. A complete history, physical examination and pertinent laboratory data were obtained for each patient. The average age of the patients was 59, and ranged from 44 to 75 years. All had abnormal electrocardiographic and ballistocardiographic findings. The characteristics of the group and the results of khellin therapy are summarized in table 1.

Placebos were not used in evaluating the effects of this drug on the various patients. A control period of two weeks preceded the administration of crystalline khellin. During this time a record was kept of the frequency of their anginal attacks and the number of glyceryl trinitrate tablets used per day. The only drugs administered during this study were glyceryl trinitrate, crystalline khellin, phenobarbital or a mixture of phenobarbital, belladonna and crystalline khellin. Control electrocardiograms and ballistocardiograms prior to medication were made both before and after exercise tolerance tests. In all instances, these tracings were abnormal. The electrocardiograms showed the usual expected findings of coronary insufficiency.

The ballistocardiograph has been utilized by others[12] in typical cases of angina pectoris, and it

* Khelloyd, manufactured by Lloyd Brothers, Pharmacists, Inc., Cincinnati, Ohio.

TABLE 1.—*Effect of Crystalline Visammin on a Controlled Group of Patients with Angina Pectoris*

Patient	Age, Sex, Race	Diagnosis	Duration of Angina	Periods of Study					Results of Treatment
				Control		Cryst. visammin		Maintenance Dose	
				Attacks per day	No. GTN* per day	Attacks per day	No. GTN* per day	mg. per day	
1.	56, M, W	ASHD†	3 yrs.	5	10	1	0	100	Increased exercise tolerance. Almost no pain.
2.	70, M, W	ASHD†, PMI‡	1 yr.	3	5	0	0	100	Free from pain.
3.	61, M, W	Hypertension	2 yrs.	2	6	0	0	50	Excellent. Free from pain.
4.	46, M, W	Hypertension	6 mo.	8	Many	3	4	300	Pain much less severe. Able to work.
5.	51, F, N	ASHD†, Recent infarct	3 yrs.	3	5	1	0	100	Pain only on exertion.
6.	69, M, N	ASHD†	18 mo.	1	2	0	0	100	Increased exercise tolerance. Free from pain.
7.	66, M, W	ASHD†	8 yrs.	1	1	0	0	50	Less fatigue. Free from pain.
8.	66, F, W	ASHD†, Severe angina	1 yr.	Many	30 plus or minus	0–4	3–4	150	Increased exercise tolerance. Pain less severe.
9.	50, M, W	ASHD†, Hypertension	8 mo.	2	3	2	3	200	Would not continue with drug because of toxic effects.
10.	75, M, W	ASHD†	2 yrs.	Many	Many	0	0–1	100	Increased exercise tolerance. Free from pain.
11.	65, M, W	ASHD†, Hypertension	3 yrs.	2	4	0	0	50	Free from pain. Increased exercise tolerance.
12.	75, M, W	ASHD†	5 yrs.	5	6–8	1	0	100	Increased exercise tolerance. No pain.
13.	57, M, W	ASHD†	3 yrs.	3	3	0	0	50	Able to return to work. Free from pain.
14.	48, F, W	Hypertension	4 yrs.	4	8	4	4	200	Refused to continue drug because of side effects.
15.	44, M, W	Hypertension, ASHD†, Myocardial infarct	1 yr.	1	2	0	0	100	Increased exercise tolerance. No pain.
16.	61, M, W	Hypertension	6 yrs.	2	2	0	0	100	Able to do much more work. No pain.
17.	53, F, N	Hypertension, ASHD†	2 yrs.	1	2	0	0	100	No pain. Breathes easier.
18.	71, F, W	ASHD†, Myocardial infarct	10 yrs.	1	3	0	0	100	No pain. Tolerates much more exercise.
19.	47, F, W	Myocardial infarct	6 mo.	0–1	1–2	0	0	50	No more pain. Able to work now.
20.	50, M, N	ASHD†	2 yrs.	2	2	0	0	50	No pain. Increased exercise tolerance.
21.	51, M, W	ASHD†, Hypertension	18 mo.	4	6	1	1	100	Pain less severe. Tolerates exercise much more.

* Glyceryl trinitrate. † Arteriosclerotic heart disease. ‡ Posterior myocardial infarct.

has been found that a definite relationship exists between the symptom complex and abnormal mechanical heart action. The arbitrary grades of abnormality established by Brown[12] were used in our studies to classify the degree of severity of involvement. According to the method, the ballistocardiograms are graded according to regularity of pattern, definity of curves, amplitude and configuration. Four grades are used, with number one

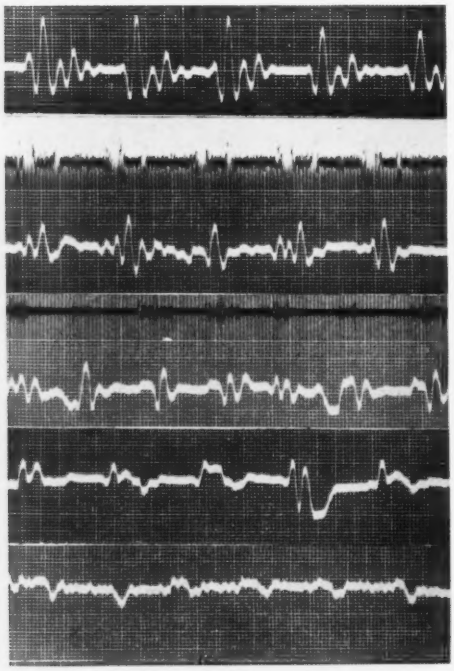

FIG. 1. The above series of ballistocardiograms illustrate first a normal tracing for comparison with others showing increasing amounts of abnormal mechanical heart action.

being the least and number four being the most abnormal (fig. 1). It was hoped that the ballistocardiograph could be utilized to obtain objective evidence of the effects of khellin on the heart. The instrument used was of a high frequency type designed by Starr[13] and was uniformly calibrated each time with a 280 Gm. weight.

The initial dosage of crystalline khellin was 200 mg. per day given in four equal 50 mg. doses. Each patient was seen weekly. If cumulative effects appeared, a two day rest period was instituted to allow these effects to disappear, and the dosage then reduced to 100 mg. per day given in two 50 mg. doses, or even to 50 mg. once a day in a few cases. Most of the patients who manifested side reactions at the 100 mg. dosage level were given a tablet composed of:

Khellin (crystalline)	50 mg.
Phenobarbital	15 mg.
Extr. of Belladonna, U.S.P.	15 mg.

The criteria used for determining improvement in the patients were a decreased number and a lessening in severity of attacks, a reduction in the number of glyceryl trinitrate tablets, an increase in exercise tolerance and an improvement in the ballistocardiographic pattern.

RESULTS

Toxicity. Dosages of 200 mg. per day of pure crystalline khellin can be tolerated by most patients for only limited periods. Reduction of the daily dose to 100 mg. in two divided doses markedly reduced the severity of the side effects. When the daily dose of 100 mg. was given in four divided doses, only four of 21 patients experienced side effects after six weeks of treatment. These four patients no longer experienced nausea when the dose was further reduced to 50 mg. daily in two divided doses.

In addition to elimination of side effects by reduction of dosage, it appears that the concomitant administration of phenobarbital may control the undesirable symptoms. In six of our series of cases, nausea and insomnia were experienced on doses of 100 mg. per day, but when the tablet containing khellin, phenobarbital and belladonna was given in equivalent dosage, side effects were eliminated in five of the cases. Furthermore, it was found that the side effects of even the higher doses could sometimes be eliminated by simultaneous administration of suitable amounts of phenobarbital. The drug had no effect on pulse or blood pressure.

Of the 21 patients studied, two were maintained on 200 mg. of the drug per day for four weeks with nervousness as their chief complaint. Another tolerated this same dosage for three weeks before the development of nausea, vomiting and nervousness. Two others were on this dosage without side effects for two weeks, and another for one week. The remainder of the 21 patients showed manifestations of vertigo, headache, diarrhea, nausea, vomiting and insomnia after only two days of

treatment on 200 mg. When the daily dosage was reduced to 100 mg. and given in two equal doses, about 50 per cent of the patients still complained of a bothersome nausea, but when it was divided into four equal doses, only four of this latter group of patients experienced side effects after six weeks of treatment. These same four patients still showed a small amount of nausea on a single 50 mg. daily dose, but this was eliminated by giving two doses daily of 25 mg. each. Two patients refused to continue taking the drug after experiencing side effects at the 200 mg. dose level. One patient with an intractable angina, which became refractive to glyceryl trinitrate, tolerated 300 mg. per day for eight weeks and complained only of a slight insomnia which was controlled by phenobarbital.

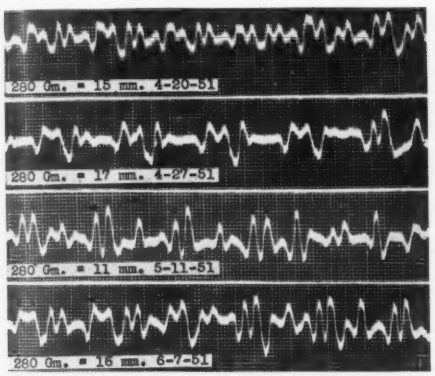

FIG. 2. Serial ballistocardiograms of a patient receiving khellin. The increase in amplitude and the improved appearance of the complexes is apparent.

Angina Pectoris. Crystalline khellin improved the cardiac status of the 19 patients who remained on the drug and invariably each patient commented on his ability to withstand more exertion. Five of the patients still experienced anginal pain. However, it was less severe and less frequent. All of these patients showed improvement for variable periods of time after the drug was discontinued. This probably can be attributed to the cumulative effect of the drug.

The control ballistocardiograms showed no common characteristic abnormality. All tracings taken during this control period were abnormal, with those nearly normal becoming more abnormal after exercise. In general, the tracings made after the crystalline khellin was administered tended to assume a more normal configuration. Calculations for cardiac output were not attempted because of the abnormality of the tracings. Cardiac strength determinations were also difficult to make and were not dependable because of the abnormality of the curves. It was of interest to note that after the patients received the crystalline khellin, their ballistocardiograms did not show the deterioration following exercise tolerance tests as they previously did before medication. Figure 2 illustrates serial ballistocardiograms of one of the patients treated. It was felt that the ballistocardiograph gave objective evidence of the favorable influence of the drug on the disease process present in these patients. No significant changes in the electrocardiographic pattern were noted during the treatment period.

COMMENT

Sufficient laboratory investigations have been conducted by competent investigators to establish the fact that this drug does reduce the tonicity of smooth muscle. The present study was primarily undertaken to compare the incidence of toxic manifestations of crystalline khellin with that of crude preparations being used to date. The pharmacologic reports on khellin by early investigators stressed the absence of toxic effects following its use. However, this was not confirmed by the clinical investigations conducted with the crude products prepared and used in this country. Anrep[14] called attention to the fact that since the publication of his observations, a considerable number of preparations of *Ammi visnaga* were being offered to the public. He warned that crude extracts of this drug could cause undesirable effects. He advised that all preparations of it which were to be used orally or parenterally should first be freed from injurious impurities and that the final concentration of the active principle should be carefully standardized. It might be concluded that the discrepancies of the earlier clinical reports with current observations may be due to the use of a drug prepared

by different methods and containing various amounts and varieties of impurities.

It was apparent from the onset of our investigations that crystalline khellin used in dosages in excess of those required to obtain the desired therapeutic effect would produce toxic symptoms similar to those obtained with the crude forms of *Ammi visnaga* used earlier. We were impressed with the fact that we were dealing with a potent drug and also realized that each patient required an individual adjustment of the amount of the drug required to relieve him of his symptoms. In this respect, this drug is not unlike digitalis.

It is universally recognized that the evaluation of the efficacy of any drug in the treatment of such a capricious disease as angina pectoris is subject to many pitfalls. The enthusiasm of the investigator for a drug frequently leads to faulty conclusions. An attempt to de-emphasize this factor was made in this investigation by using patients with the anginal syndrome who had been observed for a number of years, by evaluating the frequency and severity of attacks before and after medication, by considering the number of glyceryl trinitrate tablets used, and by utilizing objective evidence obtained with the ballistocardiograph. In this investigation the latter proved to be especially valuable because this instrument affords a physiologic approach to a physiologic problem in that it records mechanical heart action. It must be stressed, however, that this instrument was used in a qualitative manner since the tracings obtained before and after medication were still too abnormal to quantitate. The improvement in the appearance and amplitude of the complexes supplied us with evidence which is difficult to argue against. Seventeen of the 19 patients studied showed improvement in the appearance of the complexes of the ballistocardiograph.

The high incidence of unpleasant side effects observed with the use of the crude preparations of khellin in the past has limited its clinical value. Using the crystalline preparation, we were able to control the anginal symptoms in 80 per cent of the patients treated with a dose ranging from 50 to 100 mg. per day. The drug is absorbed rapidly from the stomach, and relief from the symptoms is noted within 15 to 30 minutes following its ingestion. Its cumulative effect is well established. Consequently, it is not unreasonable to assume that 50 mg. could temporarily raise the serum concentration of this drug to a toxic level. The crude preparations as used by other investigators required 100 to 300 mg. to control the anginal symptoms. However, at this level a very high incidence of unpleasant side effects was present. Therefore, it appears that the crystalline preparation eliminates toxic effects which may well be produced by the impurities present in the crude preparations.

It has not yet been established whether the toxic effects observed are produced by direct action on the gastrointestinal tract or by a central effect. Preliminary investigations are now under way to determine whether parenteral preparations would allow a higher blood concentration of this drug to be used without experiencing toxic effects. To date, six dogs have been given intravenous injections of crystalline khellin dissolved in a solution of saccharin. Each animal received toxic doses of 280 mg. of this preparation over a five day period. During this time the animals remained in good health, enjoyed a good appetite, and showed no evidence of toxicity. Five days after the last dose was given, two of the six animals died. The gross pathologic findings on these dogs at autopsy were a generalized vasodilatation and bleeding from the orifices. Further studies are now being conducted. It must be concluded that the pharmacodynamics of this drug are still little understood.

Summary

1. The action of crystalline khellin, the active principle of *Ammi visnaga*, has been evaluated in cases of angina pectoris. Dosage, therapeutic efficacy and toxicity are discussed.

2. Seventeen of the 19 patients treated with this preparation showed a good response. Two other patients discontinued therapy after the development of severe side effects.

3. Untoward reactions were minimal when 50 to 100 mg. per day of the drug were used.

This amount given in divided doses was sufficient to control the symptoms of angina pectoris in 80 per cent of the cases.

3. The results indicate that crystalline khellin is a beneficial drug in the treatment of angina pectoris. It can be used in small dosages, and in therapeutic amounts exhibits essentially no toxic effects.

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Surgical Closure of an Aortic Septal Defect

By Robert E. Gross, M.D.

Occurring just above the aortic and pulmonic valves, an aortic-pulmonary artery communication gives a left-right shunt which may be indistinguishable by clinical findings from a patent ductus arteriosus. Under some circumstances it is possible to identify the lesion by retrograde aortography. Because of increase in cardiac work, the shunt can produce cardiac strain. Whether or not the communication can be closed surgically depends upon the size of the opening and its distance above the coronary arteries. A case is here reported in which an aortic-pulmonary artery communication has been closed surgically.

CONGENITAL communication between the first parts of the ascending aorta and the pulmonary artery, just above the semilunar valves, is an uncommon lesion but deserves some consideration because it can mimic the clinical picture of a patent ductus arteriosus and because it may be possible in some instances to treat the anomaly successfully by surgical means.

In the formation of an embryo, the primitive truncus arteriosus normally becomes divided by a septum into aorta and pulmonary artery. If there is an incomplete development of this septum, an opening of variable size persists between these two great contiguous vessels and gives rise to a shunt between them. The openings have been described as generally ranging from 5 to 10 mm. in diameter, but some have been as large as 20, 30 or more mm. in maximum cross dimensions. The openings have been round, oval, triangular, or slit-like. Some have been situated very close to the orifices of the coronary arteries; others have been a centimeter or two above these vessels. Pathologic descriptions of these anomalies have been all too vague. In view of the probability that surgical correction of the anomaly can be offered some of these patients it would be helpful if pathologists who have the opportunity of studying specimens would give a more complete description of the local pathologic anatomy; in this way the surgical problems could be better understood and the best means could be devised for closing the fistulas.

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An opening between the first part of the aorta and the pulmonary artery will obviously give clinical findings quite similar to—and usually indistinguishable from—those of a persistent ductus arteriosus, which is a communication between the two systems situated somewhat further along between the vascular channels. Because of the pressure differentials, the shunt is almost invariably left to right; therefore cyanosis is seldom observed, except in terminal stages of cardiac failure. Some degree of dyspnea or diminution of exercise tolerance is often noted. Some retardation in physical development may be found. A murmur is always present; it is usually continuous, with systolic accentuation. It has been described as systolic alone, or as systolic with only a short diastolic phase. These murmurs are most intense in the second and third intercostal spaces, to the left of the sternum; they can duplicate those which originate from an open ductus. In some cases the murmur has been accompanied by a thrill. The diastolic blood pressure is somewhat reduced, and in some instances gives a pulse pressure wide enough to produce a water-hammer pulse in the arms and legs. By film and fluoroscopic studies there is evidence of a left to right shunt, giving some cardiac enlargement, fullness of the pulmonary conus, enlargement of the pulmonary artery, increased vascularity in the pulmonary bed, and a hilar dance; all of these findings are exactly those produced by an open ductus. The various clinical and roentgenologic findings probably vary in intensity from case to case, depending upon the size of the aortic leak. By electrocardiography the electrical axis may be normal, is apt to be

shifted to the left, but has been described as rotated to the right. By cardiac catheterization there is evidence of a left to right shunt into the pulmonary circuit, and the finding may be entirely those suggesting an open ductus unless the catheter can by good fortune be made to pass through the communication which lies just above the pulmonary valve; such an observation, proving the existence of an aortic septal defect, has been reported by Dexter.[3] Angiocardiography is of practically no help in differentiation from an open ductus, for both show the continued recirculation through the pulmonary circuit. Retrograde aortography has demonstrated clearly the presence of an aortic septal defect, as reported by Gasul, Fell, and Casas.[5]

At the operating table it is possible to differentiate quickly between an open ductus and an aortopulmonary window. In the former a thrill can be felt in the pulmonary artery, opposite the distal end of the aortic arch; digital pressure over the ductus abolishes the thrill. Conversely, an aortopulmonary defect gives a thrill which is most intense in the first part of the pulmonary artery, just above the pulmonary valve and within the pericardial envelope. Digital pressure in this region is necessary to shut off the thrill; compression in the area of the ligamentum arteriosum has no effect on the pulmonary artery turbulence.

Hektoen[7] gave pathologic descriptions of a case of aortopulmonary septal defect and reviewed nine others from the literature. Subsequently individual reports have been made by Fisher,[4] Oberwinter,[9] Bain and Parkinson,[1] Dadds and Hoyle,[2] Perelman and Putschar,[10] Dexter,[3] Spencer and Dworken,[11] and Gasul, Fell, and Casas.[5] An intriguing report of four cases, each found at the operating table but without attack on the lesion, was made by Gibson, Potts, and Langewisch.[6] To these is added herewith a case in which the lesion was treated surgically with success.

The patient was a 4 year old girl who was examined and treated in 1948. A cardiac murmur had been heard shortly after birth and had persisted thereafter. The cardiac impulse had always been described as being forceful. Since infancy the youngster had sweated profusely, particularly after mild exercise. There was slight exertional dyspnea, but no cyanosis. On physical examination, the child appeared to be normally developed and nourished. The blood pressure was 105/45. The heart sounds were obscured by a very loud, continuous murmur, which had marked systolic accentuation. The murmur was widely transmitted over the precordium but was most intense over the third left intercostal space, just inside the nipple line. Electrocardiographic tracings showed a mild left ventricular hypertrophy. Fluoroscopic and x-ray film studies showed the heart to be enlarged in transverse diameter, predominantly downward and to the left, apparently due mainly to left ventricular enlargement. There appeared to be moderate enlargement

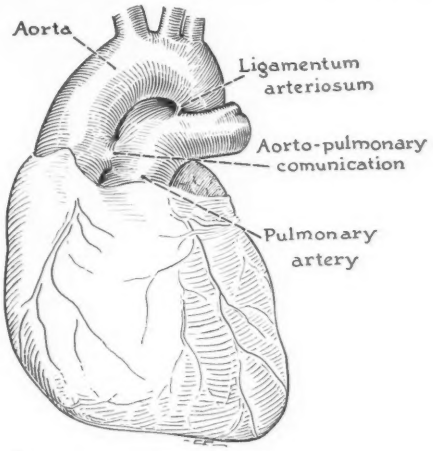

FIG. 1. Sketch showing position of congenital communication between first portions of aorta and pulmonary artery

of the left auricle posteriorly. There was bilateral pulmonary vascular engorgement with prominent hilar shadows. The left ventricular beat and the pulmonary artery beat were hyperactive. These roentgenologic findings were felt to be indicative of a patent ductus arteriosus (and indeed the murmur was thought to be typical of this condition).

Operation was advised, and exploration was carried out on May 22, 1948. A submammary exposure was made on the left, entering the chest anterolaterally in the third intercostal space, dividing the third and second costal cartilages. The pulmonary artery had a very intense and coarse thrill within it. No open ductus was found, but a fibrous ligamentum arteriosum was encountered. Digital pressure in this region did not change the thrill in the pulmonary artery. To make absolutely certain that a tiny lumen did not exist in the ligamentum, this structure was completely divided and was found to be obliterated. This in no way changed

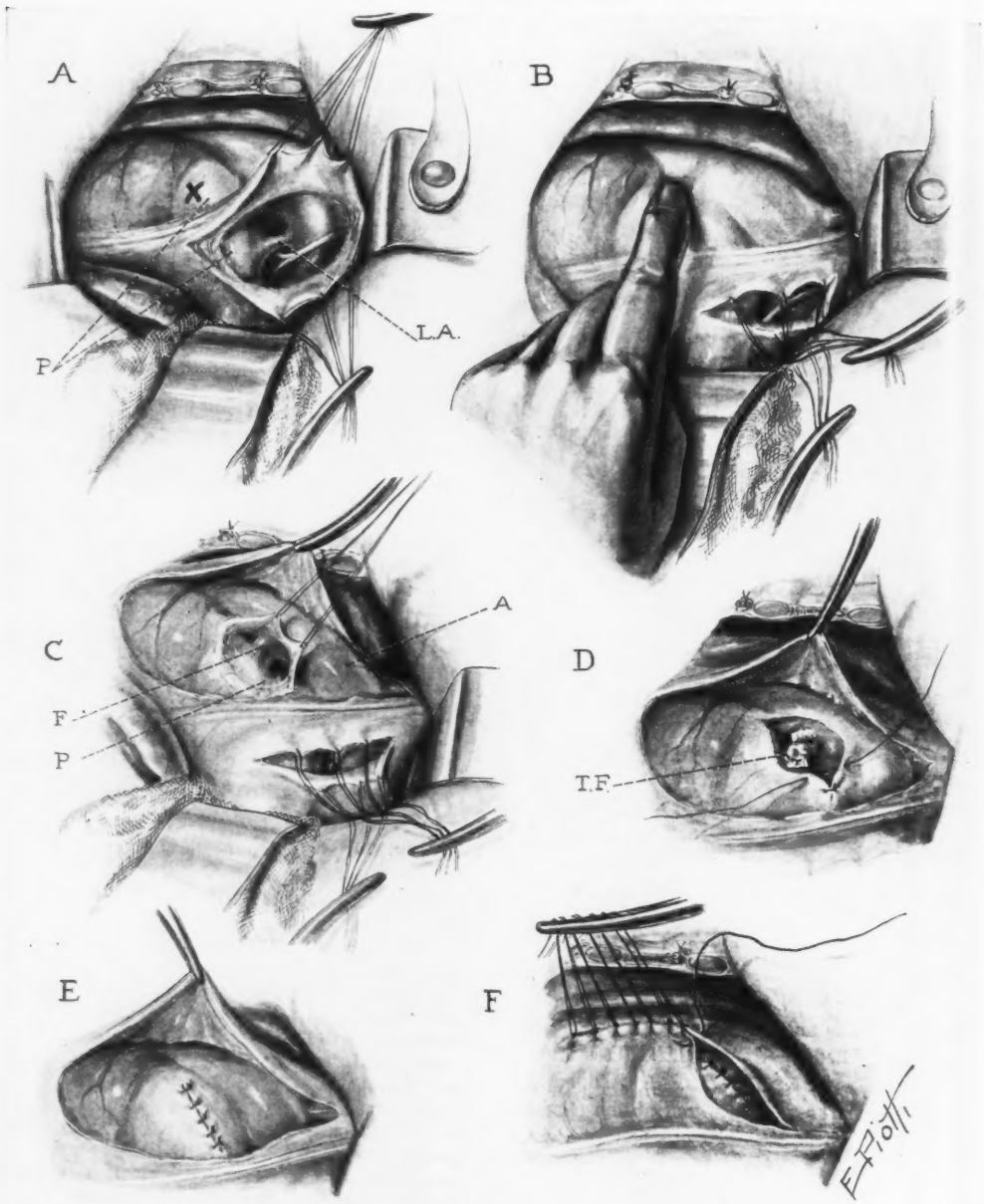

FIG. 2. Operative drawings from case here reported. *A*. Exposure through left, anteriolateral transpleural approach in the third intercostal space. L. A., ligamentum arteriosum. P., pulmonary artery. X shows the point where thrill was maximal in pulmonary artery. *B*. By digital pressure in this area, the pulmonary artery thrill could be completely abolished. *C*. Pericardium opened and held up by clamp. Epicardium opened over aortopulmonary groove and held back by sutures. A, aorta. F, fenestrum between aorta and pulmonary artery. P, pulmonary artery. *D*. Fenestrum ligated with a heavy tape. T. F. is the tied fenestrum. Epicardial stitches being started. *E*. Epicardium closed. *F*. Closure of pericardium.

the thrill in the pulmonary artery. On further examination the thrill was obviously most intense in the first portion of the pulmonary artery, just above the valve. The pericardium was now opened so that the first portions of the aorta and the pulmonary artery could be examined. The thrill was most intense at a point about 1.5 cm. above the pulmonary valve. The tip of a finger pressed into the groove between the aorta and the pulmonary artery at this level could completely shut off the thrill in the pulmonary artery. It was decided to attack surgically the fenestrum which was now known to exist between the first parts of these two vessels. The epicardium was very carefully opened and peeled back off the aorta and the pulmonary artery, to expose the underlying fistula. The great vessels lay immediately contiguous to one another and there was fear of dissecting between them because of the possibility of plunging into the thin walled communication between them and setting up bleeding which would be uncontrollable. However, it was possible to dissect down between the aorta and pulmonary artery, passing below the shunt and above the coronary arteries. After carrying this dissection toward the posterior aspect of the vessels a similar plane was opened up between the vessels above the shunt. Finally, with considerable apprehension, an aneurysm needle was passed completely around the shunt, though there was very little room between and behind the vessels to permit this. A piece of linen tape, 1.0 cm. wide, was now drawn around between the vessels, so that it encircled the shunt. At this point arterial blood began to escape from the depths of the wound so that it was evident the thin posterior wall of the shunt had been slightly torn. Believing that the one hope of controlling this situation might be to tie quickly the tape which had previously been placed, this was now rapidly and tightly drawn down. Fortunately, all of the bleeding stopped. All of the thrill in the pulmonary artery disappeared. The epicardium was closed over the ligature. The pericardium was repaired with interrupted silk sutures, making the latter closure incomplete so that any excess fluid which might accumulate in the pericardial sac could escape into the pleural cavity. The chest was closed in a routine manner. Following operation the child made a very satisfactory convalescence. She was discharged from the hospital on June 18, 1948. Frequent auscultation now showed that the prominent murmur which existed prior to operation had disappeared. To several observers no murmur existed, but one thought that a grade II systolic murmur could be heard in the pulmonary region.

Since discharge from the hospital the child has had an exceedingly satisfactory and an asymptomatic course. She has had no limitation of her physical activity. There have been no cardiac symptoms. When last examined on June 26, 1951 she was in excellent physical condition, was very vivacious, and was without complaints. Careful auscultation revealed the cardiac sounds to be entirely normal. No murmur could be heard anywhere in the thorax. At this time film and fluoroscopic examination showed only barely detectable structural abnormality of the heart; it was no longer enlarged, but there appeared to be slight left ventricular predominance. No auricular enlargement could be detected. The pulmonary artery and intrapulmonary vessels were normal in size and had normal pulsations.

FIG. 3. Photograph of patient, three years after surgical closure of an aortopulmonary opening. The child is in excellent condition. There is no murmur.

COMMENTS

The surgical exposure employed in this case was a left anterolateral approach; it certainly was not ideal, because the first portions of the aorta and pulmonary artery were retrocessed underneath the sternum, which hung over them like a shelf and interfered with the manipulations in the region. Without

doubt, a better exposure could be attained by a transverse, anterior chest incision, transversely dividing the sternum between the third and fourth costal spaces. (Indeed, we now make it a practice in all patent ductus operations to make sure that the skin of the entire anterior chest wall is prepared well toward the right anterior axillary line. Since we commonly use a left anterolateral approach, this precaution in draping would allow us to extend the incision directly across the sternum if an aortopulmonary artery fenestration is encountered when the chest is opened).

In the surgical closure of one of these aortopulmonary artery openings, simple ligation such as was employed in the above case would almost certainly not meet with uniform success. Such a ligature would in some instances incompletely close the shunt or in others might very well cut through and allow reestablishment of the fistula. It would seem to be more nearly ideal to carry out a complete division and a separation of the aorta and pulmonary artery, making a separate closure of each vessel wall. To accomplish this would require the manufacture of some appropriate clamps, one of which could conceivable be placed on the aorta to isolate the involved part of the aortic wall, while not obstructing the main aortic flow. Another similar clamp could be placed on the pulmonary vessel. It would seem that an instrument such as that ingeniously devised by Potts for performance of aortopulmonary artery anastomosis in patients with tetralogy of Fallot could be revamped to accomplish the task at hand. However, examination of the region quickly indicates that these vessels are very large, very tense, have little room between them, and are difficult to circumvent in their entirety; because of these various factors it might be nearly impossible to devise instruments which would suitably isolate appropriate portions of the aorta and pulmonary artery.

After successfully treating the above child it is felt that the fortunate outcome has been attended by a high degree of luck and that simple ligature might lead to disaster if attempted in all cases of aortopulmonary artery fenestration. In spite of its shortcomings as a universal method of treatment, the fact remains that tape ligation was successful in this patient and the method might well be employed in other suitable, selected cases.

Summary

During fetal life incomplete development of the septum between aorta and pulmonary artery can lead to persistence of an opening between the first portions of these vessels, just above the semilunar valves. Such a communication permits a left to right shunt, producing the clinical picture, roentgenologic changes, and physiologic disturbances which closely simulate those accompanying a patent ductus arteriosus. By cardiac catheterization the two conditions can be differentiated if the operator is fortunate enough to pass the catheter directly through the opening which exists between the first portions of these two major vessels. Retrograde aortography can visualize the defect. If a patient is explored, believing there is a patent ductus arteriosus, and none is found, an aortopulmonary communication can be identified by observing the point of maximum intensity of the thrill within the pulmonary artery. Digital pressure in the region normally occupied by a patent ductus will not abolish the thrill, whereas digital pressure over the groove between the first portions of the aorta and pulmonary artery will shut off the thrill.

A case is reported in which surgical attack has been made on a defect between the first portions of the aorta and pulmonary artery, this patient having been followed for three years since surgical closure. As far as is known, this is the first instance of successful surgical correction of this congenital abnormality.

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A Study of Factors Related to Effects of Quinidine in Experimental Auricular Flutter

By BARBARA B. BROWN, PH.D.

Increasing doses of quinidine cause increased slowing of the auricular rate in flutter of circus movement origin, and maximally tolerated doses cause reversion to sinus rhythm. Quinidine lengthens conduction time in the nonfluttering auricle, and the effect increases as the dose is increased. Refractory period is lengthened equally by small and large doses. Experimental results suggest that the effects of quinidine on the auriculoventricular conducting mechanisms are of three types, (1) direct depressant, (2) vagal block, and (3) reflex sympathetic stimulation, and that these effects are manifest to different degrees depending upon dose and the state of innervation to the heart.

DURING the past 30 years considerable information has been accumulated on the effects of quinidine on the heart. Much of the information was obtained indirectly. Multiple, direct leads from the heart have been used only by Lewis and his associates in 1921[1] and by Gilbert and co-workers in 1951.[2] Lewis and his associates attributed the action of quinidine in auricular flutter to its effect on refractory period. This explanation has been widely accepted. Gilbert and coworkers, however, reported that lengthened refractory period frequently but not always occurs when quinidine prevents fibrillation. The observations of Gold and colleagues[3] also conflict with those of Lewis. They found that quinidine accelerated, rather than slowed, the sinus rate and did not influence or even enhance A-V conduction which Lewis and coworkers had reported as being impaired.

In view of the conflicting data, a systematic re-evaluation of quinidine was undertaken. The actions of quinidine on experimental auricular flutter of circus movement origin were determined and were correlated with its auricular and ventricular effects as influenced by auricular rate under controlled conditions.

METHOD

The experiments were conducted in 40 dogs, weighing between 16 and 23 Kg., anesthetized by the intraperitoneal injection of 0.7 cc. per kilogram of Dial with urethane solution (Ciba). Blood pressure was recorded from the carotid artery. Auricular electrograms were recorded and the electrocardiogram was taken from pericardial tissue near the ventricular apex. Injections were made into the external jugular vein. The reported results were obtained in dogs in which the blood pressure was at least 60 mm. Hg and the rectal temperature maintained at 37 C. by external heat.

Auricular Flutter. Flutter was induced according to the method of Rosenblueth and García Ramos.[4] Either an area of right auricular wall including some auricular and inferior vena caval tissue or a small area on the body of the right auricle was crushed. Brief, rapid electrical stimulation of the auricle then initiated flutter with a regular rate in the range between 300 and 600 beats per minute. Once induced, the flutter continued at a steady rate for many hours. It was demonstrated in many experiments, using the procedure of Rosenblueth and García Ramos, that the flutter induced was of the circus movement type in which a single impulse circulated continuously around or in the vicinity of the crushed area.

Auricular Functions. The auricle was driven with electric shocks, recording at a distance from the point of stimulation. The driving frequency was increased until the maximal rate at which the auricle followed rhythmic stimuli was established. Maximal rate occurs when the interval between stimuli is just longer than that during which no response can be elicited even with high voltages, and is used as a measure of effective refractory period. Electrical excitability was measured by determining the minimal voltage required for the auricle to follow each stimulus at each of the driving frequencies employed. Speed of the recording paper was increased from 15 to 60 mm. per second so that conduction time could be measured. When effects of nerve stimulation were studied, the nerve was

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stimulated while driving the auricle at each frequency. In all determinations of auricular function, ventricular rate was recorded simultaneously.

Recording and Stimulation. Changes in electrical activity in the auricle were recorded from pairs of silver electrodes with small interelectrodal distance (2 to 3 mm.) which were clipped lightly to the auricular muscle. Stimulating electrodes were of similar design. All recordings were made by means of a four channel ink-writing oscillograph (Grass) and were made continuously during all experiments. A model 3C Grass stimulator giving square waves was employed. For auricular stimulation the pulse duration was always 1 millisecond, the frequency was varied from 2 to 15 per second, and current strength was varied from 0.5 to 15 volts. The duration of stimulation of the auricle was generally about 20 seconds or until adequate records for analysis could be taken. Maximal nerve stimulation was effected by using the lowest frequency of stimulation which slowed or accelerated the ventricle significantly and a voltage above which no further change could be produced. For the cut central end of the vagus this was stimuli of 0.2 or 0.5 millisecond duration at a frequency of 10 to 30 per second and a voltage of 10 to 20. The sympathetic chain was stimulated by placing the electrodes between the stellate and the ganglion of T-2, after freeing the chains of all connections except the postganglionic cardiac fibers arising from the stellate ganglion, using a pulse duration of 0.01 millisecond, a frequency of 2 or 60 per second, and a voltage of between 20 and 40.

Results

Auricular Flutter. The effects of increasing doses of quinidine on auricular and ventricular rates of innervated hearts are illustrated in figure 1. Maximal auricular slowing occurs within two minutes after injection. With doses of 4 mg. per kilogram, the marked slowing was usually followed by sudden reversion to a sinus rate within five minutes at a time when the auricular rate was already recovering. The ventricular rate in innervated hearts during flutter was either increased or decreased by quinidine. In general, doses of 2 mg. per kilogram increased, while doses of 4 mg. per kilogram decreased ventricular rate.

Data on the effects of different doses of quinidine on auricular and ventricular rates during flutter in both innervated and decentralized (denervated) hearts are summarized in the form of dose-response curves in figure 2. The amount of auricular slowing increases as the dose is increased from 0.5 to 4 mg. per kilogram in both innervated and denervated hearts. The action of any particular dose of quinidine on ventricular rate during auricular flutter is extremely variable in hearts with

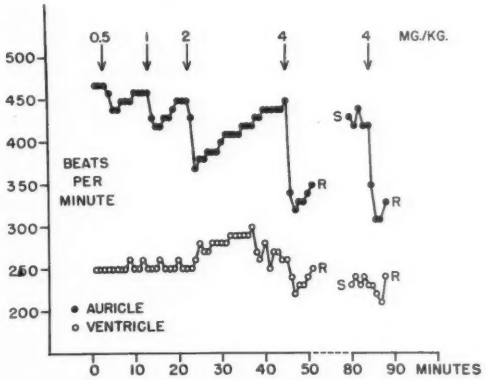

FIG. 1. Effect of increasing doses of quinidine on auricular and ventricular rates during auricular flutter of circus movement origin in a heart with intact innervation. R indicates reversion to sinus rate; S indicates stimulation to reinitiate flutter.

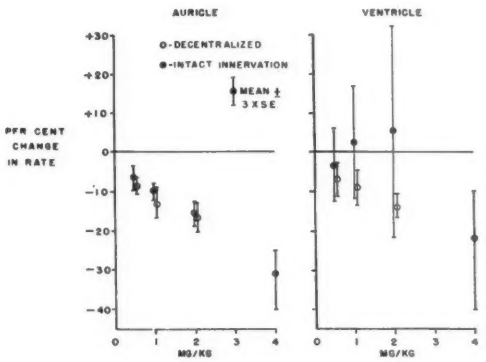

FIG. 2. Relation between dose of quinidine and effect on auricular and ventricular rates during flutter of circus movement origin both in innervated and in decentralized (denervated) hearts. Each point represents the mean for at least five determinations.

intact innervation. Slowing occurred both with small (0.5 mg. per kilogram) and with large (4 mg. per kilogram) doses, while an increased ventricular rate frequently occurred with doses of 1 and 2 mg. per kilogram. In four

experiments with innervated hearts, these four doses were given successively with an interval between injections sufficient to allow full recovery of blood pressure and of auricular and ventricular rates. The resulting dose-response curves were like those of figure 2. In three of the experiments the ventricular rate was increased at doses intermediate between the minimally effective and maximally tolerated doses. In the fourth experiment no increase of ventricular rate occurred but the slowing caused by the intermediate doses was less than that caused by the small and large doses.

When both vagal and sympathetic innervations to the heart were sectioned, quinidine always slowed the ventricular rate, and the amount of slowing increased slightly but not significantly as the dose was increased (fig. 2).

TABLE 1.—*Incidence of Reversions from Flutter to Sinus Rate Produced by Quinidine Sulfate*

Dose	Intact Innervation No. reversions / No. injections	Vagotomized and Sympathectomized No. reversions / No. injections
mg./Kg.		
0.5	0/7	0/4
1	1/8	2/7
2	1/7	1/5
4	5/5	—

The frequency of reversion from flutter to sinus rate after the injection of different doses of quinidine is given in table 1. The number of reversions produced by doses less than 4 mg. per kilogram is insignificant in both innervated and denervated hearts. When 4 mg. per kilogram was injected, reversion occurred in all of the five innervated hearts studied. The rate of injection ranged between 0.5 and 2 mg. per kilogram per minute depending upon the dose and blood pressure level. The injection rate was slower with large doses in an effort to maintain a blood pressure above 60 mm. Hg. In these experiments doses of 8 to 16 mg. per kilogram were lethal to three of eight dogs when innervation to the heart was intact, while 4 to 8 mg. per kilogram were lethal for three of five dogs in which the heart had been denervated.

Conduction Time. The time for an induced auricular wave to pass from the proximal to the distal recording leads (diagram, fig. 3.4) was measured in milliseconds directly from the electrograms (14 experiments). Figure 3.4 illustrates the increased conduction time at all auricular rates produced by 2 mg. per kilogram of quinidine. The effect increased as the dose was increased, and maximally tolerated doses of 8 mg. per kilogram doubled conduction time.

Refractory Period and Excitability (14 Experiments). As the driving rate is increased, the

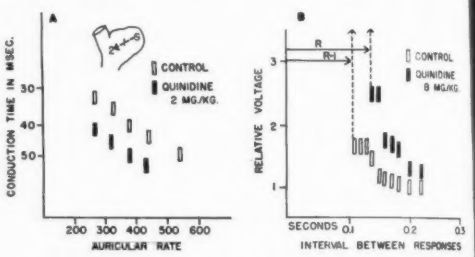

FIG. 3. *A.* Effect of quinidine on auricular conduction time as related to auricular rate. Limits of error are indicated by lengths of bars. S in diagram of auricle is point of stimulation; 1 and 2 are pairs of recording leads.

B. Effect on auricular excitability in terms of voltage relative to that required at the lowest auricular rate. Auricular rate is indicated as its reciprocal, that is, interval between beats. R-1 and R indicate shortest intervals between effective stimuli before and after quinidine, and are an estimation of effective refractory periods.

interval between responses is shortened, and voltage required for the auricle to follow repetitive stimuli is increased until an interval is reached at which conducted responses fail to occur. This is a measure of effective refractory period and is indicated in the graph of figure 3*B* by the arrows R. Doses of 8 mg. per kilogram increased thresholds to electrical stimulation, especially at high auricular rates, and lengthened the effective refractory period by 30 to 40 per cent. Doses of 2 mg. per kilogram caused a similar lengthening of effective refractory period but did not significantly alter auricular excitability.

Ventricular Rate. The effect of quinidine on ventricular rate was investigated in 20 dogs according to the procedure previously de-

scribed by Brown and Acheson.[5] The auricle was driven by electric shocks at frequencies varying between 200 and 600 per minute. The relation between ventricular rate and auricular rate was expressed as the ratio V/A, and plotted against the auricular rate (fig. 4). The resulting curves indicate the decreasing ability of the ventricle to follow the auricle as the auricular rate is increased; ventricular-auricular ratio (V/A) decreases from 1.0 to 0.5 and below.

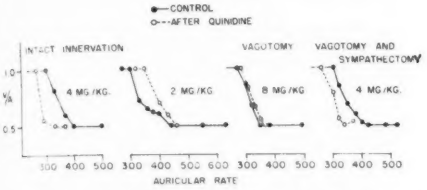

FIG. 4. Examples of the different effects of quinidine on the ratio of ventricular to auricular rate (V/A) at different auricular rates in hearts with different states of innervation.

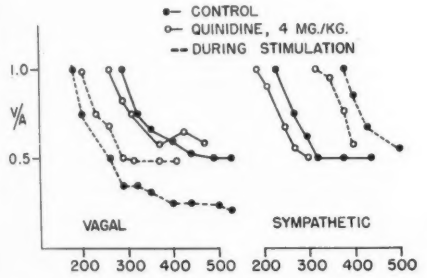

FIG. 5. Effect of quinidine on the ratio of ventricular to auricular rate (V/A) at different auricular rates in decentralized hearts with and without vagal and sympathetic stimulation. Auricular rates in beats per minute are given on the abscissas.

When innervation to the heart was intact, doses of 4 mg. per kilogram of quinidine decreased the ability of the ventricle to follow the auricle as illustrated in figure 4. The effects produced by smaller doses of 2 mg. per kilogram were variable. In two of four experiments this dose increased the ventricular-auricular ratio (V/A) at increasing auricular rates (fig. 4), while in a third experiment it was decreased, and in a fourth this ratio was unchanged.

Following vagotomy, doses of 4 and 8 mg. per kilogram (fig. 4) caused little or no change in the ventricular-auricular ratio (V/A) at the different auricular rates. In two experiments, repeated doses of 8 mg. per kilogram at 30 minute intervals failed to alter the ventricular-auricular curve.

When both vagal and sympathetic nerve supplies to the heart were eliminated, doses of 4 and 8 mg. per kilogram regularly decreased the ventricular-auricular ratio (fig. 4). The same doses of quinidine also impaired the depression of ventricular rate produced by vagal stimulation (fig. 5), although the magnitude of effect varied from animal to animal and was greatest at rates of auricular stimulation above 300. Similarly, the enhancement of ventricular-auricular ratios during sympathetic stimulation was also impaired (fig. 5).

DISCUSSION

Soon after Drury and Iliescu[6] first demonstrated that quinidine slows the rate of auricular flutter and fibrillation, Lewis and coworkers[1] investigated the effects of quinidine on refractory period and conduction in the dog's auricle by direct measurement, and postulated that reversion from flutter occurred because of a lengthened refractory period. These authors considered the marked slowing of conduction time, but concluded that circus movement was terminated by quinidine only in those cases in which lengthening of refractory period predominated over slowed conduction. The recent report by Gilbert and associates[2] stated that, while lengthening of refractory period was the most marked change coincident with termination of postfaradic fibrillation, it was not necessarily an accompaniment.

The influence of refractory period on the mechanism of reversion in circus movement flutter was studied recently by Brown and associates.[7] Employing compounds which consistently lengthen refractory period, it was found that (a) compounds with little effect on conduction time are more likely to cause reversions of circus movement flutter, since the rapidly moving impulse meets refractory tissue, and (b) compounds which lengthened

conduction time cause marked slowing of flutter with little tendency to reversion, since there is an adequate interval for recovery from refractoriness in the circuit. The latter relationship appears to hold true for doses of 0.5 to 2 mg. per kilogram of quinidine. Larger doses cause no greater lengthening of refractory period than small doses, but they do cause significantly greater prolongation of conduction time. This would seem to mean that these doses of quinidine would not cause reversions but would merely slow the flutter. Actually, doses of 4 mg. per kilogram consistently cause reversions. The reversions consistently occurred after the peak of conduction velocity slowing (fig. 1). This suggests that recovery from lengthened refractory period proceeds more slowly than recovery from slowed conduction velocity. At the time of maximal slowing of conduction velocity, the gap between head and tail of the impulse is wide enough for flutter to continue. While the mechanisms underlying conduction time begin to recover, the effective refractory period remains lengthened. The result is a shortening of the gap until it is obliterated and reversion occurs. The present investigation thus suggests that the Lewis hypothesis holds true, and that whether or not reversions occur (in experimental circus movement flutter) depends upon the temporal relation between effects of quinidine on refractory period and on conduction velocity. Following the oral administration or intravenous infusion of quinidine a different relationship could exist.

Experiments done in this laboratory indicate that quinidine may also markedly slow auricular flutter induced by aconitine according to the method of Scherf. The degree of auricular slowing in these experiments also parallels the amount of slowing of conduction time; however, the auricular electrogram frequently becomes disorganized and may even briefly increase in rate when small doses are administered. Additional evaluations employing aconitine-induced flutter are required before its action in different auricular arrhythmias can be understood.

The ventricular effects of quinidine are due to varying combinations of direct depressant action and its action on the innervation, both of which in turn are dependent upon the dose. Previously, effects of dosage have received little attention and no differences in the effects of different doses have been reported. Regarding innervation, Megibow and Katz[5] reported that during faradically maintained auricular fibrillation quinidine depressed A-V conduction in the denervated heart through a direct action but that enhancement occurred in the innervated heart by reflex vagal action arising from vasodepression.

Large doses of quinidine depress the ability of the ventricle to follow the auricle both in innervated and in denervated hearts. Small doses affect ventricular rate similarly. These results can be explained by a direct depressant action of quinidine on auriculoventricular conduction mechanisms. In innervated hearts, doses intermediate between the minimally effective and the maximally tolerated ones often increase ventricular rate during auricular flutter and also may increase the ventricular-auricular (V/A) curves in the nonfluttering heart, while both are depressed in denervated hearts by these doses. In addition, intermediate and large doses partially block the effect of vagal stimulation on ventricular rate. These results indicate that a second action of quinidine is that of vagal block. Further, reflex action via the sympathetics is suggested because the ventricular rate is unaffected in vagotomized hearts by doses which cause depression of the ventricular-auricular (V/A) curve in innervated and in denervated hearts. Since quinidine partially blocks the ventricular effects of sympathetic stimulation, the data suggest that the depressant action may be functionally antagonized by this reflex action. Stated more simply, small doses are adequate to cause direct depression but not to cause effects on the innervation; intermediate doses produce partial vagal block and probably reflex sympathetic action which are of such degree that the direct depressant effect is often obscured, while the direct depression obtained with large doses of quinidine is greater than effects on the innervation.

Summary

Auricular Effects. Increasing doses of quinidine cause increased slowing of auricular rate in flutter of circus movement origin. Maximally tolerated doses cause reversion to sinus rhythm. In the nonfluttering auricle quinidine lengthens conduction time and the effect is increased as the dose is increased. Refractory period was lengthened similarly by both large and small doses. The threshold of auricular excitability was raised only by large doses and generally only at high auricular rates.

Ventricular Effects. When both vagal and sympathetic nerve supplies to the heart were sectioned, quinidine always impaired the ability of the ventricle to follow the auricle, and slowed the ventricular rate during auricular flutter. Ventricular rate was unaffected when the sympathetics were intact and the vagi were cut. In hearts with intact innervation large and small doses depressed ventricular rate while the effect of intermediate doses was variable.

Acknowledgment

The author is indebted to Dr. George Acheson of the Department of Pharmacology, College of Medicine, University of Cincinnati, for his interest and advice, and to Mr. M. Jack Keyl and Mr. James A. Goldey for technical assistance.

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Observations on the Atria of the Human Heart by Direct and Semidirect Electrocardiography

By R. WENGER, M.D., AND D. HOFMANN-CREDNER, M.D.

By evaluation of direct electrocardiographic leads from the right atrium and semidirect esophageal leads from the left atrium, "atriodiagrams" have been constructed for both atria. The spread of activation in the atria has been studied under normal conditions as well as in cases of mitral heart disease, cor pulmonale, etc. In cases of doubtful enlargement of the left atrium, esophageal electrocardiograms may be helpful for diagnosis. In six cases of auricular flutter the results were not uniform.

THE DEVELOPMENT of cardiac catheterization[1, 2] has enabled various authors[3–15] to investigate the human heart by direct electrocardiography. In the present paper we have used this method for recording the potentials of the inside of the right atrium. Also the introduction of esophageal leads into clinical electrocardiography[16–38] has opened a wide field of research. These leads are especially valuable in studying the left atrium since they constitute semidirect leads of this chamber.

Our investigations were performed by means of ordinary cardiac catheters which contain a wire and so represent an electrode. For esophageal leads we used an electrode with a selector switch, which enabled us to take 11 leads from different points in the esophagus without moving the electrode.[39] Ten normal subjects and 40 patients with various cardiac diseases were studied.

An essential feature of direct and semidirect leads from atrial muscle is the intrinsic deflection of the P wave. The theory of Lewis that these deflections correspond to the time when activation passes the electrode has been attacked by various authors. Recent experimental findings, however, speak in favor of the opinion that it is not inaccurate to use the intrinsic deflections in both intracardiac and esophageal leads as an indication of the time of arrival of the process of activation under the electrode.[40–42]

We have attempted to develop a simple mathematical formula for these relations. For the purpose of excluding, as far as possible, the influence of different heart rates, we have correlated the interval from the beginning of the intrinsic deflection of the P wave to the beginning of the QRS complex as measured in a simultaneously recorded lead II (referred to as the i-Q interval) with the P-Q interval. Obviously the ratio P-Q/i-Q is increased when the activation of the point under the electrode is retarded and decreased when the reverse occurs. We examined this ratio in 40 normal persons by statistical methods[22] and found that the average value was 1.7 (standard deviation 0.164). It never exceeded 2.0. In 10 cases with enlarged left atria the quotient was 2.49 (standard deviation 0.32). We recommend this method for use in cases of doubtful enlargement of the left atrium (mitral heart disease, left ventricular hypertrophy, congenital heart diseases, advanced pregnancy with elevated diaphragm). We constructed atriodiagrams for both atria by using the distances from the diaphragm to the electrode as ordinates and the ratio P-Q/i-Q as abscissas. We are fully aware of the difficulties which arise from the fact that we could localize our endoatrial electrode only by means of orthodiagrams made in one plane. Figure 1 shows the construction of an atriodiagram.

It has been stated by various authors[7, 8, 14]

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that in the right atrium there may be a difference in the appearance of the intrinsic deflections in the cranial and the caudal portions of the atria of as much as 0.06 second. The atriodiagram of the right atrium shows in most cases a fairly typical pattern. The line determined by the values discussed in the preceding paragraph descends from the upper left to the lower right quadrant. The very first activation in many cases may be seen at the point which more or less corresponds to the region of the sinus node. The activation of the uppermost region of the right atrium is sometimes 0.01 to 0.02 second later than that of the region of the sinus node.

The normal pattern of the left atriodiagram, recorded by means of esophageal leads, is entirely different from that of the right atrium. There is no marked obliquity of the line forming the diagram. This means that different points of the posterior wall of the left atrium normally become activated at approximately the same time. This diagram represents a more or less vertical line which only shows slight bulges or spikes. Figure 2 shows the diagrams of several normal subjects.

In four patients who showed a P mitrale we found an almost normal diagram for the right atrium, whereas the diagram for the left atrium showed a broad bulge. This confirms the opinion that local retardations of the conduction in the left atrium cause the widening and notching of the P wave in leads I and II.[43] In figure 3 the esophageal diagram is widely deformed between 6 and 14 cm. above the diaphragm.

In one patient who showed a P pulmonale we found on the right as well as on the left side an almost normal atriodiagram (fig. 4). This supports the assumption that the pulmonary P wave is due less to retardation of conduction than to variations of the local potentials, especially in the right atrium.

There are examples in which patterns of the right atriodiagram differ from the normal pattern in that caudal regions of the atrium become activated earlier than more cranially situated portions. In one patient who showed such a diagram there was also a partial right bundle branch block which furnished further evidence for the assumption of local disturbances of conduction in this case. We could not find any sign of atrioventricular rhythm in this patient. As far as we know, there is at present no other way of diagnosing such local disturbances of conduction in the right atrium (fig. 5*A*).

In the left atrium there may also be other causes of deformity of the atriodiagram. In one case of postdiphtheritic paresis there was a broad and notched P wave in leads I and II. The esophageal leads revealed that in this case the deformity of the P wave was not accompanied by a bulging of the left atriodiagram, as it has been shown in cases of P mitrale. The left atriodiagram showed a curve which closely corresponded to that of a normal right atrium (fig. 5*B*). Therefore there was a considerable delay of conduction in the middle and caudal portions of the left atrium. The absolute values of the ratio did not exceed 2.0.

Auricular Flutter

There is no need to discuss the various theories of the mechanism of auricular flutter. The two main theories attribute the disturbance to (1) a circus movement[44–49] and (2) frequent recurring stimuli.[50–51]

We examined six cases of auricular flutter. In three of these cases we could record intracardiac and esophageal leads simultaneously. In two of these cases there were very remarkable findings: the quotient in the esophageal leads showed a continuous prolongation from points near the diaphragm to the uppermost portions of the left atrium. The values in the right atrium, where the direction of conduction was normal, agree, when brought into correlation with values of the esophageal electrocardiogram, with the assumption of a closed circus. Figure 6 shows the finding in one of these two cases in a schematic illustration. In table 1 the i-Q values of the case are presented.

Discussion

The method of obtaining "atriodiagrams" from both atria makes it possible to compare the conditions of conduction in the atria. As mentioned before, the atriodiagram of the

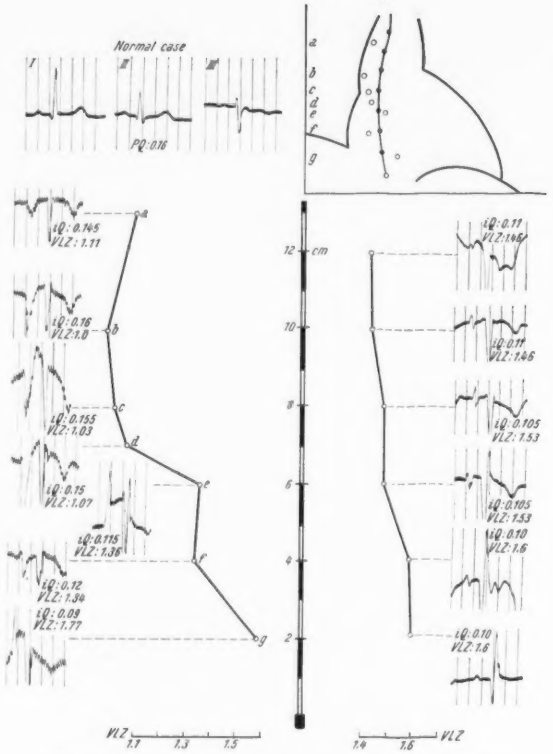

FIG. 1. On the left side is the atriodiagram of the right atrium as constructed from the values obtained by endoatrial leads from the right atrium. On the horizontal line are the P-Q/i-Q ratios, on the vertical line the heights of the various points above the diaphragm in centimeters. A direction from the left superior to the right inferior corner of a diagram therefore means that the respective atrium becomes activated in craniocaudal direction. *VLZ* (Vorhofleitungszahl) corresponds to the ratio P-Q/i-Q, as explained in the text.

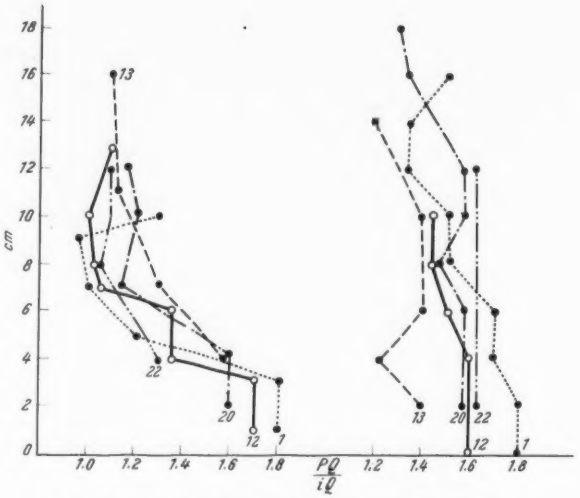

FIG. 2. On the horizontal line the ratios P-Q/i-Q (see text) are recorded. In the vertical direction are shown the distances of the intracardiac and esophageal electrodes from the diaphragm, as determined from orthodiagrams. The left part of the figure shows the diagram obtained from the right atrium (increasing retardation of the intrinsicoid deflection in craniocaudal direction). On the right side the diagram constructed from the esophageal leads shows a more or less vertical direction.

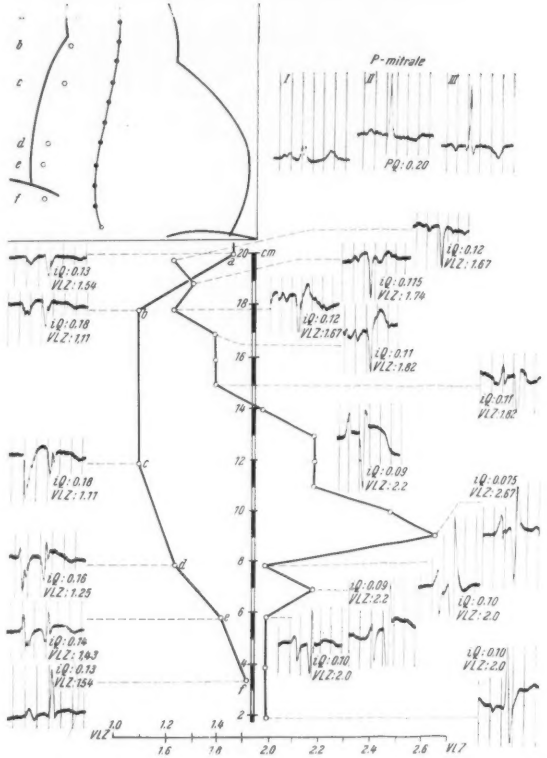

FIG. 3. Mitral heart disease. P mitrale. *Left side:* the diagram obtained from the right atrium shows a more or less normal pattern. *Right side:* the esophageal diagram for the left atrium bulges widely toward the right. *VLZ* (Vorhofleitungszahl) corresponds to the ratio P-Q/i-Q, as explained in the text.

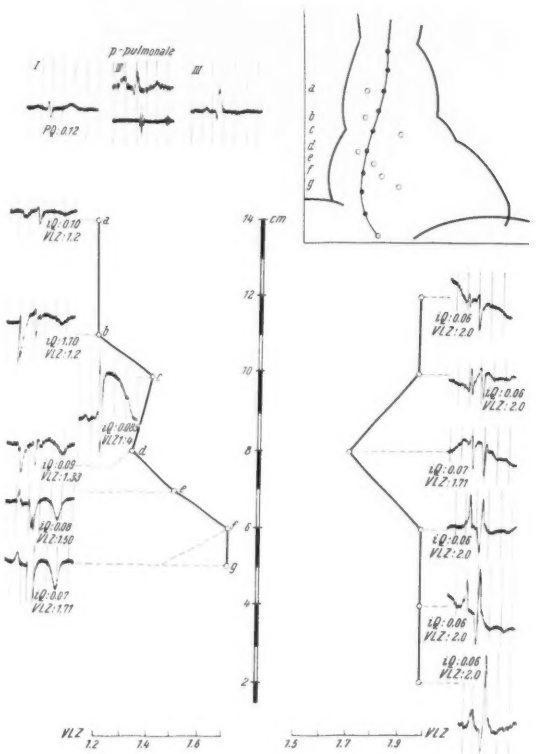

FIG. 4. P pulmonale. The diagrams for both the right and the left atrium are more or less normal. *VLZ* (Vorhofleitungszahl) corresponds to the ratio P-Q/i-Q, as explained in the text.

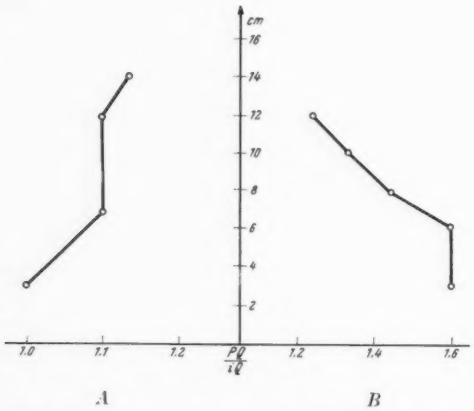

FIG. 5A. Abnormal right atriodiagram from a patient with arteriosclerotic coronary artery disease. The direction is the reverse of the normal and indicates that more caudally situated regions of the right atrium are activated earlier than more cranial ones. This is perhaps a sign of local conduction disturbance.

FIG. 5B. Abnormal left atriodiagram from a patient with postdiphtheritic paresis. Leads from caudal portions of the esophagus, which is close to the left atrium, show activation much later than leads from the cranial portions. This is regarded as a sign of local conduction disturbance in the caudal part of the left atrium.

right atrium reveals a craniocaudal direction of activation, whereas the atriodiagram of the left atrium shows no time differences at various levels above the diaphragm. Probably the excitation wave coming over from the right atrium reaches the left atrium at different points above the diaphragm more or less at the same time. It might be objected that this finding in the esophageal leads is due to the fact that there is a distance of a few millimeters up to 1.0 cm.[52, 53] between the muscular wall of the left atrium and the esophagus. However, there are instances (as in local disturbances of conduction or in auricular flutter) where the pattern of the left atriodiagram is entirely different from the normal; we judge from this that the diagram reflects relatively objectively the course of activation of the left atrium.

The findings in two of our cases of auricular flutter would agree with the theory of circus movement. Our records speak in favor of the

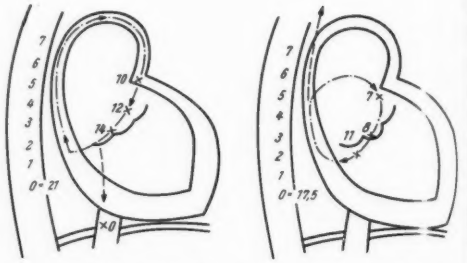

FIG. 6. Schematic illustration of a sagittal section through both atria in two cases of auricular flutter. Each number corresponds to 0.01 second and is related to a zero point at the base of the left atrium. (See table 1.) The numbers are obtained by simultaneous esophageal and endoatrial leads. The finding in these two cases are compatible—with certain restrictions—with the hypothesis of circus movement.

TABLE 1. *Tabulation of Values Shown in Figure 6*

	Esophagus		Right Atrium	
	i-Q	i-Q reduced	i-Q	i-Q reduced
cm.				
16	0	7	0.18	10
14	0.01	6	0.16	12
12	0.02	5	0.14	14
10	0.03	4		
8	0.04	3		
6	0.06	1		
4	0.07	0		

Length of a cycle is 0.21 second.

The i-Q distances in the esophageal leads are reduced to a value 0 for the inferior part of the left atrium (right column). In the right part of the table the i-Q distances of three points of the right atrium are registered. They are reduced in the same way as the esophageal values (see also fig. 6).

assumption that a wave of activation ascends in the region of the left atrium, as registered in the esophageal electrocardiogram, and descends in the right atrium. It is not possible to judge from these facts what would be the exact course of the circulating stimulus. The fact that different leads obtained at about the same heights above the diaphragm on the anterior wall of the right atrium reveal the same i-Q interval speaks in favor of the opinion that there would be a relatively broad circulating wave.

The form of the P wave also agrees with the conception of a circus movement in the mentioned direction. In the esophageal leads we found QS patterns of the P waves in the low, RS patterns in the middle and R patterns in high regions of the retroatrial esophagus. In the right atrium the same change of patterns was to be seen, but, just as in normal cases, in the reverse direction, from the region of the superior vena cava to the region of the inferior vena cava. In the regions of both venae cavae, as well as in the uppermost parts of the left atrium, there seemed to exist smaller waves of activation, which might be interpreted as secondary waves leaving the main or mother wave. This would correspond to the experimental findings of Lewis.[47, 48] The four other cases showed different findings, which would speak more in favor of another mechanism of excitation.*

Summary

Direct leads from the right atrium obtained by cardiac catheterization and semidirect leads from the left atrium obtained by esophageal leads were recorded simultaneously in 50 human subjects. The normal appearance of the "atriodiagram" has been studied in 10 normal subjects.

The different paths of activation of both atria, as shown by these investigations, are discussed. The activation of the right atrium proceeds in a craniocaudal direction, whereas the left atrium becomes activated in a more or less right to left direction.

The pattern of the atriodiagrams in cases showing P mitrale and P pulmonale are shown. In cases showing P mitrale there is a typical deformation of the left atriodiagram, indicating a local delay of activation in the left atrium. In cases showing P pulmonale there seem to be no greater disturbances of conduction.

The method makes it possible to diagnose local disturbances of conduction in the right as well as in the left atrium. It may also be helpful in cases of doubtful enlargement of the left atrium.

The results of our investigations on six cases of auricular flutter are briefly discussed. The results were not uniform in all six cases. However, they are interpreted to show that a circus movement might be present in some of the cases of auricular flutter.

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Certain Inevitable Relationships among the "Unipolar" Extremity Leads

By PAUL H. LANGNER, JR., M.D., J. MALVERN BENJAMIN, JR., M.S., AND SAMUEL R. MOORE, M.D.

It is demonstrated in this paper, both mathematically and experimentally, that the scalar sums of the three "unipolar" extremity leads when recorded with resistors of high value in the neutral network must equal zero if all the possible sources of error are eliminated. However, this fact has no bearing upon the validity of the Einthoven hypothesis or upon the theoretic concepts underlying the Wilson central terminal. In fact, when any three points are chosen at random to make a central terminal and the potential differences between each of the three points in turn and the central terminal are recorded, the scalar sum of these potential differences will invariably equal zero. It is also shown why any augmented "unipolar" extremity lead must be exactly 50 per cent greater than the respective unaugmented "unipolar" extremity lead if properly recorded.

IT IS the purpose of this paper to discuss two properties of the three "unipolar" extremity leads[1] commonly used in electrocardiography. The two properties are:

(1) The algebraic sum of the potential differences recorded by the three "unipolar" extremity leads must equal zero.

$$V_R + V_L + V_F = 0$$

(2) An augmented "unipolar" extremity lead[2] must be 50 per cent larger than the respective unaugmented "unipolar" extremity lead.

$$aV_R = \tfrac{3}{2} V_R$$
$$aV_L = \tfrac{3}{2} V_L$$
$$aV_F = \tfrac{3}{2} V_F$$

We shall demonstrate that these two properties must be true independent of the validity of the Einthoven hypothesis. Therefore, this paper has no bearing upon the validity of the Einthoven hypothesis.[3-6] This discussion is undertaken because differences of opinion have been expressed regarding the nature of the relationships expressed in (1) and (2).

It seems to be a rather common belief that since the sum of the "unipolar" extremity leads is zero, the Wilson central terminal must be a zero potential electrode. On the other hand, the opposite point of view has also been expressed. Katz[7] writes that, "This deviation [of the central terminal from zero] can be readily demonstrated by algebraically adding the sum of V_L, V_R and V_F. Theoretically their sum should equal zero if they are truly 'unipolar' leads in an equilateral triangle. Actually this is not true and often their sum is far removed from zero." Simonson and Keys[8] state "The crux of the theory is the assumption that the algebraic sum of the true absolute potentials for the recording positions of the three limbs is equal to zero."

When one first considers that the algebraic sum of the voltages recorded by the three "unipolar" extremity leads must equal zero, it may be difficult to see why this does not prove that the Wilson central terminal itself is at field zero.* However, it will be shown below that when any three points on the body are connected to form a central terminal and then leads are taken by recording the potential difference between this central terminal and each of the three points in turn, the algebraic sum of the potential differences recorded in these three leads will be zero. Thus, the successful performance of this experiment will do no more than verify this mathematical relationship. It will not throw any light on the degree to which the Wilson central terminal

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* There has never been any misconception about this point in the original papers by Doctor Wilson and his colleagues whose mathematical analyses have always been beyond criticism.

itself approaches a true field zero potential. The type of experiment necessary to explore the degree to which the Wilson central terminal approaches field zero potential would have to be one which checks the degree to which the Einthoven hypothesis is approximated by conditions existing in the living human body.

Another related problem that has recently appeared in the literature pertains to the relationship between the augmented and unaugmented "unipolar" extremity leads. Simonson and Keys[8] studied this problem and concluded that, "A quantitative comparison between V and aV leads revealed such tremendous variability of the augmentation ratio both interindividual and between leads in the same individual that standards obtained with V leads are not applicable to aV leads and vice versa." This conclusion seems to be incorrect in light of our experimental observations and our analysis of the circuits involved. It can be shown both mathematically and experimentally that an augmented "unipolar" extremity lead must be 50 per cent larger than the respective unaugmented "unipolar" extremity lead, provided no error in technic has been made, the phase of respiration in which the leads are taken is the same, and the effect of skin resistances has been minimized.

Experimental Demonstration

When the three "unipolar" extremity leads, either augmented or unaugmented, are recorded simultaneously on a three channel instrument the areas under the deflections must add up to zero for any given heart beat provided no technical error has occurred. In fact, one can attach the three lead wires intended for the right arm, left arm and left leg to any three points on the body, record three leads with the lead selector switch set at V_R, V_L and V_F in turn, or aV_R, aV_L and aV_F in turn, and the sum of the deflection in either set of three leads so recorded will add up to zero provided respiratory phase and other possible variables are controlled. When either set of three such leads is recorded consecutively on a one channel instrument, as is usually the case, the phase of respiration must be exactly the same or the deflections may not add up to zero because of a change in position of the heart from lead to lead. Another fundamental condition that must be provided for, whether the leads are recorded simultaneously or consecutively, is the equalization of the resistors in the neutral network of the central terminal.[9, 10] Because of the possible variation in the resistance between a limb electrode and the tissues beneath the electrode, ideally these neutral network resistors should have very high values so that the skin-electrode resistance variations will constitute only a small fraction of the total resistance in each branch of the neutral network. In routine work we must compromise in our choice of the value of these neutral network resistors, because as these resistances are increased in value, the recording system becomes more and more susceptible to alternating current interference pickup, while, on the other hand, as we reduce the value of these resistances, the possible error in the neutral point due to the differences in contact resistances at the limbs becomes greater. In most of our experiments we used the traditional 5000 ohm resistors but in six experiments 50,000 ohm resistors were used.

In the study to demonstrate the fact that the algebraic sum of the "unipolar" extremity leads must equal zero we proceeded as follows: In two individuals, using three channels of a four channel Sanborn polyviso, 20 series of three points were taken at random and the electrodes normally placed on the three extremities were placed on each of the 20 series of three points. Then records were made by setting channel 1 on aV_R, channel 2 on aV_L, and channel 3 on aV_F.* Inspection of the resulting tracings showed that the sum of the three leads so recorded was approximately zero but precise measurement was not possible when large deflections occurred in a small space of time. This factor becomes obvious when one places a ruler along a rapidly rising deflection. It is not possible to decide whether the measurement is 5 mm. or 10 mm. because

* We chose the augmented "unipolar" extremity lead for purposes of convenience but the demonstration is equally applicable to the original "unipolar" extremity lead.

the deflection seems to occur almost instantaneously. To solve this problem a two channel cathode ray oscillograph with an expanded time scale was employed since we did not have a suitable three channel instrument available. In two individuals, six experiments were performed in which three points were selected so that they were all markedly positive (near V_5)

FIG. 1. Three points were selected so that they were all markedly positive to field zero. Each lead shown is the potential difference between each point in turn and the central terminal formed by the junction of the other two points through 50,000 ohm resistors. The algebraic sum of the three instantaneous voltages on each of the eight vertical time axes is zero (±0.5 mm.).

or all markedly negative (near V_2) with regard to field zero. This fact was verified by checking the potential value of each point against the Wilson central terminal. Records were made using a two channel lead selector switch with 50,000 ohm resistors in the neutral networks, leading into the two channel cathode ray oscillograph. The subject was in a shielded and grounded room to avoid 60 cycle interference. Leads were recorded as follows: The lead selector switch was placed on aV_R for channel 1 and aV_L for channel 2. Then a second pair of leads was made with the switch on aV_L for channel 1 and aV_F for channel 2. Thus a common lead was present in each pair of tracings to permit comparison of all three leads in the same phase. A typical experiment is illustrated in figure 1. In figure 1 the two common leads have been superimposed so as to give the illusion of a three channel recording. Eight vertical lines intersecting each complex at the same phase have been drawn. The value of the deflections at the point of intersection of each vertical line was measured and added. Measurements were made to the nearest half millimeter. In every case the sum of the deflections was within 0.5 mm. of zero.

In our study, to demonstrate the fact that an augmented "unipolar" extremity lead is 50 per cent larger than the same unaugmented "unipolar" extremity lead, records were made from 25 individuals in the recumbent position. As far as possible the position of the heart was controlled in each individual by recording all leads in the same phase of held respiration. Five thousand ohm resistors were employed in the circuit of the central terminal. The deflections recorded by V leads were made directly comparable in magnitude to those recorded by aV leads, by making the standardization for the former 50 per cent greater than for the latter. This technic is more accurate than attempting to compare the two types of leads with the same standardization for each. Fifteen tracings were recorded on the Sanborn Visocardiette with standardization for the aV leads set at 8 mm. = 1 mv., and for the V leads, 12 mm. = 1 mv. Ten tracings were recorded by a DuMont Cathode Ray Oscilloscope, type 304-H, using a Sanborn preamplifier built especially for this oscilloscope. The cathode ray was photographed by a Westinghouse Oscilloscope Camera, Model ph 33671-1. The standardization for the aV leads was $1\frac{1}{2}$ inches = 1 mv., and for the V leads, $2\frac{1}{4}$ inches = 1 mv. This degree of vertical amplification and a film speed of approximately 330 mm. per second produced records which reveal the electrocardiographic deflection in much greater detail than seen in conventional electrocardiograms.[11]

Occasionally minor variations occurred between individual complexes in the two types of

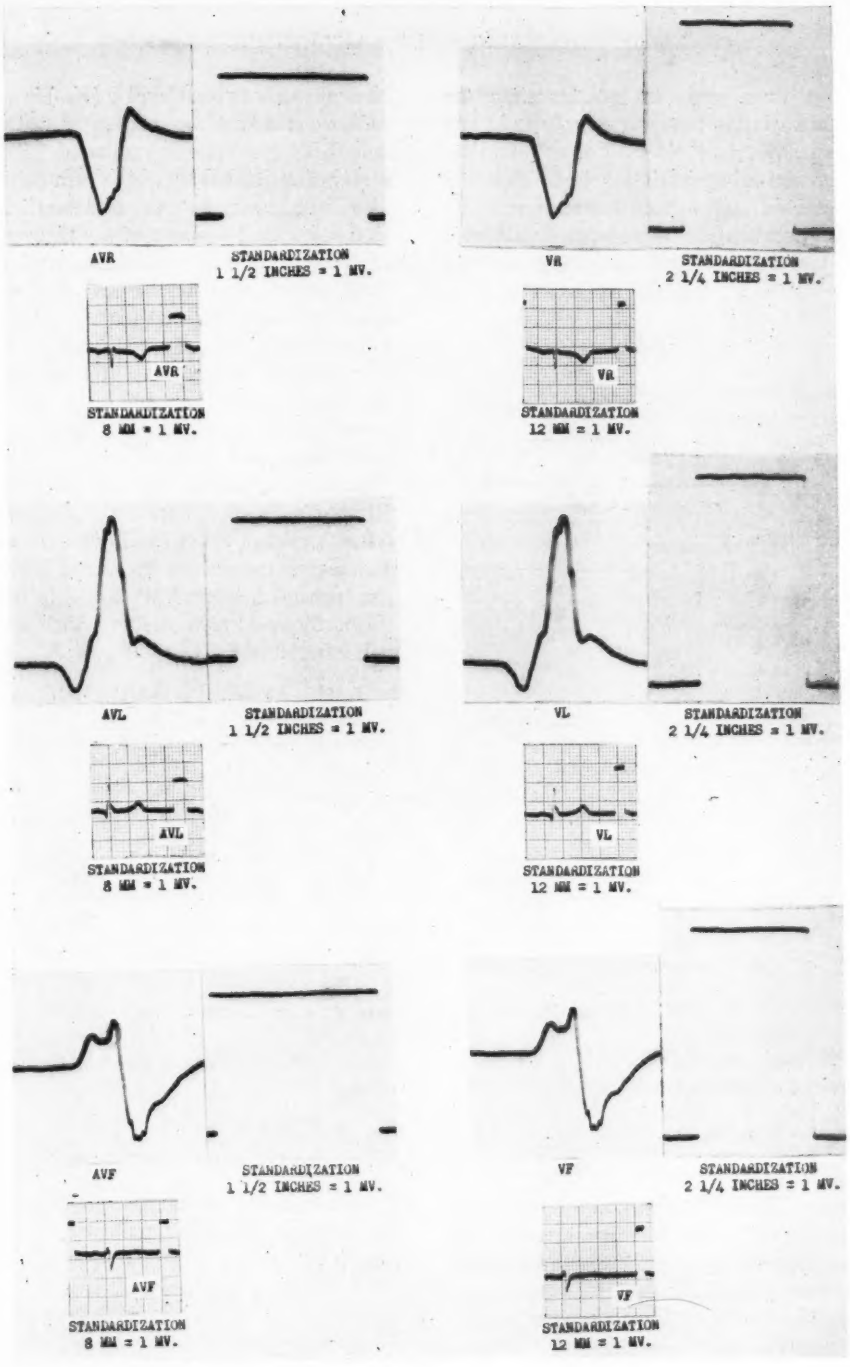

FIG. 2. Two sets of three "unipolar" extremity leads are illustrated. The leads are labeled. The large leads were made with a cathode ray oscillograph and expanded time scale. The small leads were made on a visocardiette. The standardization for the unaugmented leads is one and one-half times that for the augmented leads. It will be seen that when so recorded each augmented lead is practically identical to the respective unaugmented lead demonstrating that the augmentation ratio is 50 per cent.

leads, but these were no greater than the individual variation between complexes in any single lead. Within the limits of standardization error and minor variation to be expected in consecutive tracings there was no measurable difference between the V leads, recorded with an amplification one and one-half times that used for aV leads, and the aV leads in both

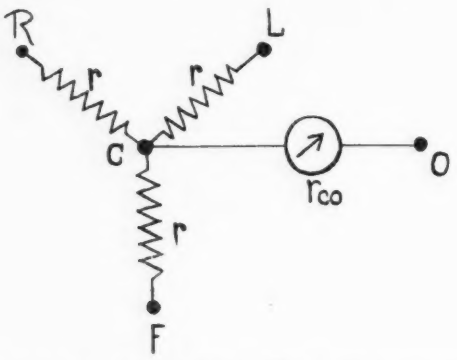

FIG. 3. Circuit diagram of the "unipolar" extremity leads. See text for discussion.

the voltage between C and O (V_{CO}) is a measure of how closely C approximates a true "field zero." This voltage is measured with a voltmeter of resistance, r_{CO}, high compared with r. It will be shown by the mathematical derivation below that the sum of the three extremity leads, each paired with the central terminal, must equal zero regardless of the voltage existing between the central terminal and the point O, the infinitely distant field point. In fact, the sum of any three voltages taken from any three points on the body will be zero when paired with a central terminal derived from these same three points.

Turning again to figure 3, with the aid of Kirchoff's Second Law* we may write the following set of equations in which the symbol V_{AB} means the voltage measured between any two points A and B. Point A is arbitrarily taken to be always positive with respect to point B. Thus $V_{AB} = -V_{BA}$.

$$\left.\begin{aligned} V_{RO} + V_{OC} + V_{CR} &= 0 \\ V_{LO} + V_{OC} + V_{CL} &= 0 \\ V_{FO} + V_{OC} + V_{CF} &= 0 \end{aligned}\right\} \quad (1)$$

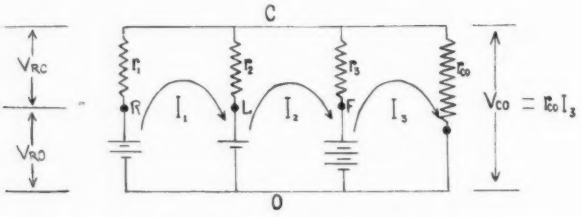

FIG. 4. Rearrangement of circuit diagram shown in figure 3.

magnitude and contour. Figure 2 shows a typical result of such a comparison.

CIRCUIT ANALYSIS

Proof that $V_{RC} + V_{LC} + V_{FC} = 0$

Referring to figure 3, let R, L and F represent points on the right arm, left arm and left leg respectively, while C represents the Wilson central terminal formed as illustrated using three equal resistors (r).* O represents a field point infinitely distant from R, L and F. Thus,

Adding these equations and rearranging terms we get

$$V_{RC} + V_{LC} + V_{FC} = V_{RO} + V_{LO} + V_{FO} - 3V_{CO} \quad (2)$$

It now remains to be proved that the right side of this equation is identically equal to zero. That is,

$$V_{RO} + V_{LO} + V_{FO} - 3V_{CO} = 0$$

or

$$V_{CO} = \frac{V_{RO} + V_{LO} + V_{FO}}{3}$$

* In this analysis it is assumed that r is large compared with skin resistances. For analysis of the effect of skin resistance when this is not the case, the reader is referred to reference 9.

* The sum of the voltage drops must equal the sum of the voltage rises around any closed loop.

This can be more easily demonstrated from figure 4 which is the circuit of figure 3 rearranged. The voltages within the body that appear at the three extremity points R, L and F are represented as batteries to make the complete circuits more apparent, and the resistors shown in figure 3 still occupy the same electrical positions.

Solving this circuit by the use of mesh currents, I_1, I_2, and I_3, and letting $r_1 = r_2 = r_3 \equiv r$, we write:

$$\begin{aligned} V_{RO} - V_{LO} &= 2rI_1 - rI_2 \\ V_{LO} - V_{FO} &= -rI_1 + 2rI_2 - rI_3 \\ V_{FO} &= -rI_2 + (r + r_{co})I_3 \end{aligned}$$

From which

$$I_3 = \frac{V_{RO} + V_{LO} + V_{FO}}{r + 3r_{co}}$$

and

$$V_{CO} = r_{co}I_3 = \frac{r_{co}}{r + 3r_{co}}(V_{RO} + V_{LO} + V_{FO})$$

Since $r_{co} \gg r$, this reduces to

$$V_{CO} = \frac{V_{RO} + V_{LO} + V_{FO}}{3}$$

Thus equation (2) becomes

$$V_{RC} + V_{LC} + V_{FC} = 0$$

Let us next consider the augmented leads. Let aV_{RC} be the voltage between R and C in figure 3 when the resistor r between R and C is removed. Proceeding as we did in expressing equations (1) we write

$$aV_{RC} + V_{CO} + V_{OR} = 0$$

or

$$aV_{RC} = V_{RO} - V_{CO}$$

Once again we solve the circuit of figure 4 for V_{CO}, this time letting r_1 become infinite and $r_2 = r_3$. For this case

$$V_{CO} = \frac{V_{LO} + V_{FO}}{2}$$

so

$$aV_{RC} = V_{RO} - \frac{V_{LO} + V_{FO}}{2} \qquad (3)$$

Similarly

$$V_{RC} = V_{RO} - V_{CO}$$

or

$$V_{RC} = V_{RO} - \frac{V_{RO} + V_{LO} + V_{FO}}{3}$$

Multiplying this equation by $\frac{3}{2}$ we obtain

$$\frac{3}{2}V_{RC} = \frac{3V_{RO} - V_{RO} - V_{LO} - V_{FO}}{2}$$

$$\frac{3}{2}V_{RC} = V_{RO} - \frac{V_{LO} + V_{FO}}{2} \qquad (4)$$

We see that the left hand sides of equations (3) and (4) are identical. Equating the right hand sides and multiplying by $\frac{2}{3}$ we obtain the desired result.

$$V_{RC} = \tfrac{2}{3}aV_{RC}$$

Similarly it may be shown that

$$V_{LC} = \tfrac{2}{3}aV_{LC}$$

and

$$V_{FC} = \tfrac{2}{3}aV_{FC}$$

Combining the results of the two sections of this analysis, it also follows immediately that

$$aV_{RC} + aV_{LC} + aV_{FC} = 0$$

Summary and Conclusions

There are two properties of the "unipolar" extremity leads:

(1) The algebraic sum of the potential differences recorded by the three "unipolar" extremity leads must equal zero.

$$V_R + V_L + V_F = 0$$

(2) An augmented "unipolar" extremity lead must be 50 per cent larger than the respective unaugmented "unipolar" extremity lead.

$$\begin{aligned} aV_R &= \tfrac{3}{2}V_R \\ aV_L &= \tfrac{3}{2}V_L \\ aV_F &= \tfrac{3}{2}V_F \end{aligned}$$

It is believed by some that the existence of these two properties is directly related to the Einthoven hypothesis.

We have shown both by experimental demonstration and by circuit analysis that these two properties are inevitable consequences when any three points are connected to form a central terminal, and then leads are

taken between this central terminal and the three points successively. Therefore, these two properties have no bearing upon the validity of the Einthoven hypothesis, nor upon the question of whether the Wilson central terminal is at field zero potential throughout the cardiac cycle.

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Studies Utilizing the Portable Electromagnetic Ballistocardiograph

II. The Ballistocardiogram as a Means of Determining Nicotine Sensitivity

By HARRY MANDELBAUM, M.D., AND ROBERT A. MANDELBAUM, M.D.

Persons who have failed to habituate to the cardiovascular effects of nicotine will demonstrate changes in their ballistocardiogram after smoking. These ballistocardiographic changes produced by smoking are of more abnormal quality and are found more frequently in patients with coronary artery and hypertensive heart disease than in normal subjects. The ballistocardiograph provides an accurate objective means of determining whether nicotine has a deleterious effect upon the myocardial function of a patient. In a significant proportion of patients with heart disease who demonstrated an abnormal ballistocardiographic response to smoking, clinical improvement was obtained after a period of tobacco abstention.

THE deleterious effects which tobacco may have on patients with heart disease have been given considerable study by various investigators. The peripheral vasospastic action of nicotine has been proved conclusively by Roth.[1] Graybiel and his co-workers[2] and Roth[1] have shown the great frequency with which nicotine, either by inhalation or by intravenous administration, can cause electrocardiographic changes consisting of tachycardia and decrease of T-wave amplitude. The T-wave changes are similar to those found after atropinization. It is likely that the action of nicotine on the vagus and sympathetic ganglions is the cause of the electrocardiographic, blood pressure and pulse rate changes. These observations have been recorded in normal subjects after smoking as well as in patients with heart disease. Cases in which the use of tobacco caused angina pectoris associated with electrocardiographic changes have been described[3-5] but are considered of infrequent occurrence. Ralli and Oppenheimer[5] consider that tobacco angina results from vasoconstriction of the coronary arteries. Graybiel and his co-workers[2] believe that it is due to a sudden increase in the work of the heart, as shown by the increase in heart rate and blood pressure.

In other reports,[6-8] abstinence from smoking for extended periods of time has resulted in a decrease in the severity or frequency of the attacks of angina pectoris, as well as an occasional reversion to normal of the electrocardiogram. While the fact that nicotine can affect the cardiovascular dynamics in certain susceptible persons has been well established, a great deal of doubt[9,10] has been cast upon the importance of absolute abstention from smoking in the routine care of patients with heart disease. On the other hand, many clinicians agree with Moschcowitz[7] that, because of the angiospastic[11] action of nicotine, along with the clinical experience that many patients with angina pectoris do well after the cessation of smoking, more attention should be paid to nicotine sensitivity in the study of patients with heart disease.

A satisfactory test to determine which patients are sensitive to tobacco is needed. That there is individual susceptibility[4, 9, 10] to nicotine has been established. Blood pressure rises of 22 mm. Hg systolic and 20 mm. Hg diastolic as well as increases in heart rate of 50 beats per minute have been described following smoking.[4] No significant difference in the degree or relative frequency of these blood pressure or heart rate changes has been found in persons with heart disease compared with normal subjects. Retinal spasm was noted in hyper-

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tensive patients as an effect of nicotine.[12] Mathers and his associates[9] believe that an increase in the heart rate of more than 25 beats per minute may be regarded as the most reliable index of hypersensitivity to the immediate effects of nicotine.

It is an accepted fact that nicotine affects the cardiodynamics of particular individuals by causing tachycardia, an increase in the blood pressure and occasionally changes in the electrocardiogram. A more impressive test, however, would be one that demonstrates a direct effect upon the subject's myocardial efficiency. In doing ballistocardiographic studies upon subjects with neurocirculatory asthenia, essential hypertension and coronary artery disease, we have observed that a number of patients showed definite changes in their ballistocardiograms following smoking. These changes in the ballistocardiographic pattern demonstrated in almost every case that the ventricular ejection wave was of abnormal quality. Ballistocardiographic changes after smoking were found also in several persons who were apparently without heart disease. All of the ballistocardiograms were made with the direct electromagnetic ballistocardiograph previously described[13] upon subjects who had rested for 15 minutes, who had not eaten for three or more hours, and who had not smoked for 24 hours. After the completion of a ballistocardiogram taken under resting conditions, the subjects were asked to smoke their particular brand of cigarette or cigar. Many subjects did not care to finish more than half of the cigarette or an inch of the cigar. Positive tests were noted as frequently after abbreviated periods of smoking as when the entire cigarette or cigar was smoked. Positive tests were also occasionally found when the particular cigarette used was of the "denicotinized" variety. No note was made as to whether or not the subject inhaled. The postsmoking ballistocardiogram was taken two minutes after the completion of smoking and was followed immediately by a ballistocardiogram taken after the performance of a modified two-step exercise test.[13]

Levy and his co-workers[10] used the Nickerson ballistocardiograph to estimate changes in cardiac output in response to smoking. Their findings were a generalized fall in cardiac output in normal subjects, averaging 1.8 per cent of the presmoking output, and a rise in cardiac output in persons with heart disease, averaging 6.4 per cent. No follow-up studies were done in these patients with heart disease who were sensitive to nicotine to determine whether the cessation of smoking would result in an improvement of the presmoking resting ballistocardiogram or in any subjective relief of angina. Furthermore, it is of interest to note that in their study no significant changes were found in the electrocardiograms after smoking of the subjects who were sensitive to nicotine, as determined by the ballistocardiogram and the pulse rate changes. In a recent study, Caccese and Schrager[14] have described abnormal changes in the ballistocardiographic records of persons with and without heart disease following cigarette smoking. The Dock[15] electromagnetic ballistocardiograph was the recording instrument in the latter report.

In our studies on subjects suspected of sensitivity to tobacco, three characteristic patterns could be recognized in the ballistocardiograms as a positive reaction to smoking: (1) the hyperkemic* response; (2) abnormal variation in the inspiratory-expiratory complexes; and (3) the diminished HIJ and prominent K pattern.

A group of subjects, consisting primarily of normal subjects, of persons with complaints of palpitation, and of subjects previously diagnosed as having neurocirculatory asthenia, demonstrated the hyperkemic response in which the amplitude of the HIJK complexes became increased; an associated tachycardia was the rule (fig. 1). However, we did not consider these hyperkemic responses as evidence of a harmful nicotine effect unless some abnormal configuration was noted in the ballistic pattern as well. The hyperkemic nicotine response, however, contributed to or was the cause of symptoms such as palpitation, chest pain, dizziness or throbbing headache, in many of these persons.

The second type of abnormal smoking test

* *Hyperkemia* indicates increased velocity of ejection of blood from the ventricles, causing larger amplitude of the ballistic record.

was the development of increased respiratory variation in the ballistocardiogram, with complexes of poor amplitude in the expiratory phase (figs. 4, 6). Occasionally, all the complexes in the ballistocardiogram became bizarre and of low amplitude, resulting in a Brown classification[16] of grade 3 or 4. These findings were more common in subjects with angina pectoris. No such findings were recorded in normal controls.

Particularly in hypertensive subjects, the abnormal configuration in response to smoking was the appearance of the diminished HIJ deep K pattern[13, 17] (figs. 3, 6). In many, this change occurred only in the expiratory phases of the ballistocardiogram.

Changes in the ballistocardiogram following exercise, similar to these specific nicotine effects of increased respiratory variation with complexes of poor amplitude in the expiratory phase and/or the appearance of the low HIJ deep K pattern, have been previously described[13, 18, 19] in subjects with hypertension and coronary artery disease whose basal tracings had been normal or only slightly abnormal. In subjects suspected of sensitivity to smoking, where the immediate postsmoking ballistocardiogram showed no variation from the basal ballistocardiogram, exercising immediately after smoking demonstrated an abnormality where a previous exercise test was not abnormal. These instances, however, were not common.

It is not our purpose, in this report, to determine the statistical frequency of nicotine sensitivity in any particular group of subjects, but rather to emphasize that the ballistocardiograph appears to be of great clinical importance in the recognition of those persons who have never adapted themselves to the toxic action of nicotine. The more serious types of ballistocardiographic abnormalities resulting from smoking occurred most frequently in subjects who had coronary artery disease. There is no question, however, that people who have no heart disease may exhibit abnormal ballistocardiograms in response to smoking[14] (fig. 1). In a series of 50 subjects, from 16 to 60 years of age, who by all standards were believed to be without heart disease, 28 per cent demonstrated an abnormality in their ballistocardiogram following smoking. All of these positive ballistocardiographic smoking tests were obtained from persons less than 40 years of age. No sex difference in smoking response was noted. In persons with coronary artery or hypertensive heart disease, most of whom demonstrated an abnormal presmoking ballistocardiogram, we have found the incidence of positive smoking tests to be more than twice that obtained in persons without heart disease.

Since the ballistocardiogram represents primarily the initial cardiac output velocity of blood ejected from the ventricles, which depends entirely upon myocardial vigor, the development of ballistocardiographic abnormalities following smoking in the cardiac patient is of clinical importance. The physician responsible for the guidance of a patient with coronary artery disease or hypertension, upon recognizing a change suggestive of impaired myocardial efficiency in the ballistocardiogram following the smoking test, should be insistent that this patient stop smoking.

As a concomitant finding with the ballistocardiographic changes, we have also observed the rises in blood pressure and the tachycardia noted by other observers in response to smoking. However, we have found positive ballistocardiographic smoking tests in the absence of a rise in the heart rate or blood pressure (fig. 5; upper two traces). Not infrequently, nicotine tachycardia was associated with a ballistocardiogram which did not demonstrate any abnormality in configuration and which was considered normal. Many of the patients with positive smoking test ballistocardiograms had electrocardiographic studies done following smoking. Only two of 35 patients with angina pectoris so tested demonstrated significant electrocardiographic changes after smoking. Several patients, following a short period of smoking, complained of nausea and dizziness. The fact that all tests were done on fasting subjects may account for the frequency of these symptoms. In all subjects with these complaints, ballistocardiographic abnormalities were found. In 10 subjects, who were observed for several hours, ballistocardiographic ab-

normalities could be recognized in tracings taken from five minutes to as long as 45 min-

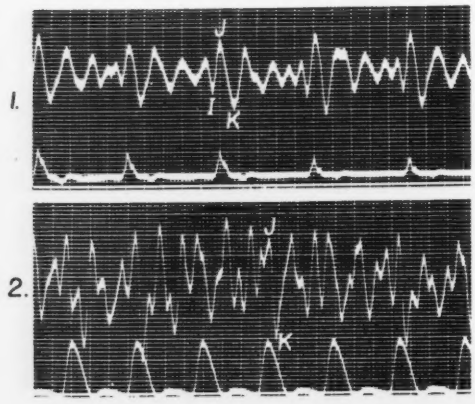

FIG. 1. Discussed in case reports.

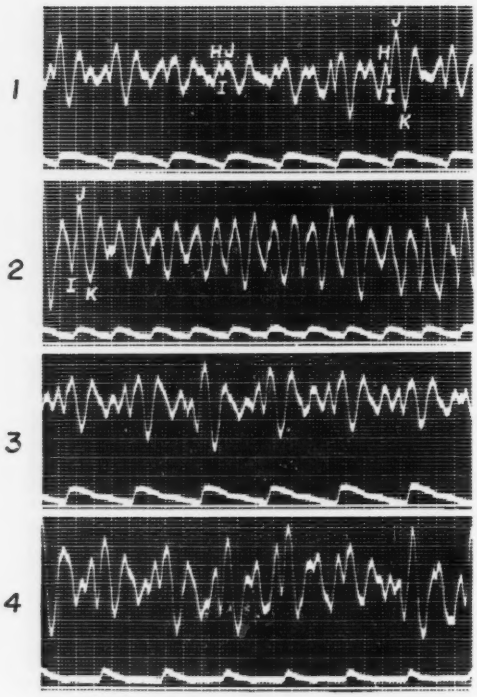

FIG. 2. Discussed in case reports.

utes after smoking had been completed. The average time required for the postsmoking ballistocardiogram to return to the resting state was 10 minutes.

The fact that tobacco can cause added distress in subjects with coronary artery-hypertensive heart disease, in whom the ballistocardiogram shows an increase in abnormality with smoking, was confirmed clinically by the subjective improvement in 30 out of 35 patients with the anginal syndrome after abstention from nicotine. Eight of these 35 patients showed improvement in either their resting or their postexercise ballistocardiogram after abstaining from nicotine for two months. Four young subjects with hypertension (fig. 5) and

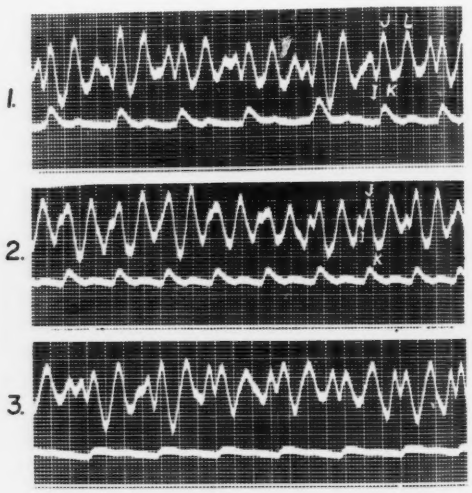

FIG. 3. Discussed in case reports.

early, deep K-stroke patterns[13] in the resting ballistocardiogram, who had positive smoking tests, responded to a period of nicotine abstention by the improvement to normal of the basal ballistocardiogram and appreciable decrease in their blood pressure.

White[20] believes that there is a condition justifiably called "tobacco heart" but that it is primarily a functional derangement and not an organic heart disease. We have observed two nondiabetic normotensive women in the fifth decade of life (fig. 2) who had complaints characteristic of coronary artery disease. Both had normal electrocardiograms and abnormal resting ballistocardiograms; after the smoking test, the ballistocardiograms showed a progression in the degree of abnormality. These

women became asymptomatic and were found to have almost normal ballistocardiograms at rest and after exercise after two months of abstention from nicotine. Whether the continued use of tobacco by these two patients who had failed to habituate to nicotine would have played a role in the development of organic heart disease is a matter of conjecture.

Illustrative Case Reports

Case 1 (fig. 1); Hyperkemic Response.* A. W., male, 32 years of age, weighing 155 pounds. This patient, a heavy smoker, suffered from attacks of

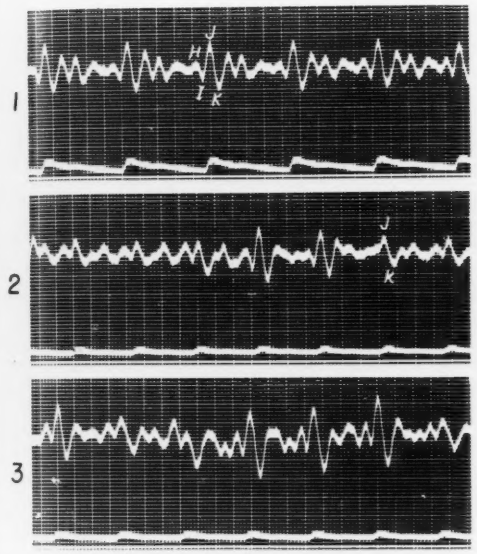

Fig. 4. Discussed in case reports.

dizziness accompanied by tinnitus and nausea. Occasional attacks of palpitation often accompanied or preceded the dizziness. His blood pressure was 140/80. Physical examination, roentgenogram of the chest, electrocardiogram and basal metabolism studies were normal. *1.* The basal ballistocardiogram was normal. *2.* After smoking half a cigarette, tachycardia occurred; the blood pressure rose to 150/90 and a ballistocardiogram with abnormal respiratory variation was obtained. The patient felt completely well during the entire test period. The increased amplitude of the K and L waves puts this nicotine response in the hyperkemic category.

* The upper channel in each figure represents the ballistocardiogram; the lower channel, the concomitant tracing taken from the left radial pulse. The J wave is recorded at the apex of the radial pulse.

Note the diminished IJ amplitude in the fourth and seventh complexes. This patient has been without complaints since giving up the use of tobacco.

Case 2 (fig. 2); Hyperkemic Response and Tobacco "Heart Disease." S. S., female, 46 years of age, weighing 114 pounds. This patient was a heavy smoker and complained of headaches, palpitation and angina on effort. The attacks of angina had been increasing in frequency and degree, forcing her to give up her work. Her blood pressure showed lability, varying from 140/85 to 185/98. Physical

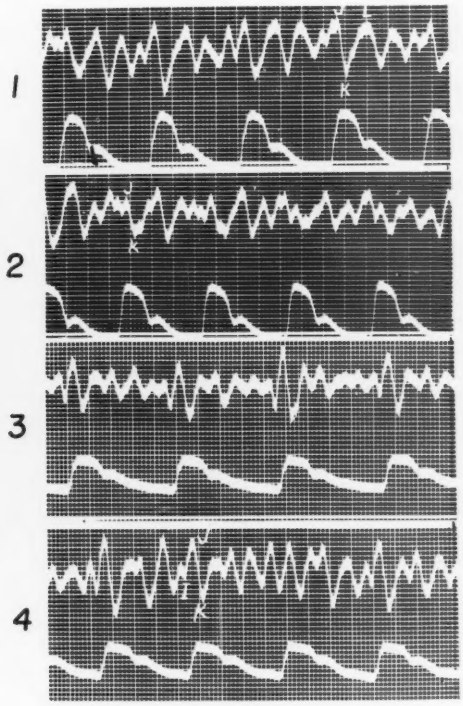

Fig. 5. Discussed in case reports.

examination, roentgenogram of the chest, electrocardiogram and basal metabolism were normal.

On March 25, 1951, *1*, the basal ballistocardiogram shows grade 2 respiratory variation with low HIJ waves in the expiratory phase. *2.* After smoking, note the tachycardia and the large amplitude of the complexes which characterize the hyperkemic response; the slurred and short HIJ strokes are evident in the expiratory phase.

The patient has not smoked since March 25, 1951, and has been free of complaints since May 15, 1951. On May 29, 1951, *3*, the basal ballistocardiogram shows marked improvement; notched J waves are present in the expiratory phases. *4.* After performance of the exercise test, short HIJ

waves can be noted in the second and fifth complexes.

Case 3 (fig. 3); Essential Hypertension; Characteristic Low HIJ Deep K Response. S. G., male, 52 years of age, weighing 186 pounds. This patient has been a heavy smoker for many years and complained of recurring headaches. His blood pressure over a period of years showed marked lability, 170/90 to 210/105. Physical examination and roentgenogram of the chest were normal. The electrocardiogram showed left ventricular hypertrophy. *1.* The basal ballistocardiogram shows normal respiratory variation with tall L waves. *2.* After smoking half a cigarette; note the short HIJ strokes especially in the expiratory phases, which gives prominence

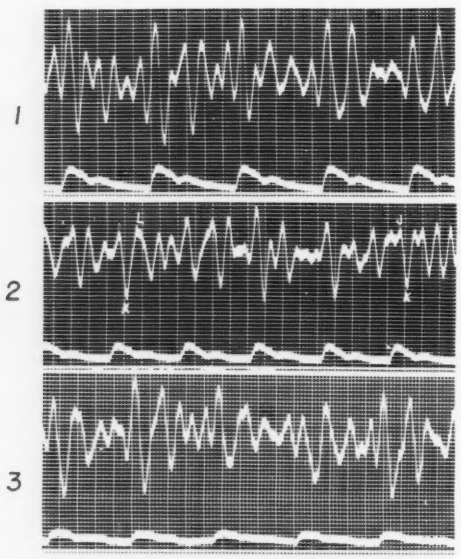

FIG. 6. Discussed in case reports.

to the K wave. *3.* The next morning; no smoking for 24 hours. A ballistocardiogram taken after performance of a two-step exercise test. (The basal ballistocardiogram preceding the two-step exercise was the same as the original.) The HIJ deflections are decreased in amplitude but not to the extent produced by nicotine. This patient improved clinically after cessation of smoking; his blood pressure has not risen above 165/90.

[*Case 4 (fig. 4); Angina Pectoris; Increase in Inspiratory-Expiratory Variation.* L. H., male, 41 years of age, weighing 181 pounds. Since his discharge from the Army, he has been aware of angina on effort. Of late, the attacks required nitroglycerin for relief. He had reduced his smoking and used denicotinized cigarettes. Many examinations and repeated electrocardiograms were normal. His blood pressure was 128/84. Physical examination, roentgenogram of the chest, electrocardiogram and basal metabolic rate were normal. *1.* Basal ballistocardiogram normal. *2.* After smoking (a denicotinized cigarette was used in this instance) the inspiratory-expiratory variations permit classification of grade 2 after Brown. *3.* After abstaining from smoking for 24 hours, the exercise test showed the inspiratory-expiratory variation to be grade 1 according to Brown. This patient has had diminished frequency of angina since losing weight and giving up smoking.

Case 5 (fig. 5); Angina Pectoris; Essential Hypertension; Improvement after Abstinence. I. L., female, 41 years of age, weighing 188 pounds. Her complaints were of angina of effort, which in the last few months had become of more frequent occurrence and of greater severity. Hypertension was of at least five years' duration.

On January 4, 1951, the blood pressure was 190/105. Physical examination, roentgenogram of the chest and basal metabolism were normal. The electrocardiogram showed left axis deviation. *1.* Basal ballistocardiogram was classified grade 1 after Brown. The fourth complex shows a notched J wave; the short HIJ deep K pattern is in evidence. *2.* After smoking, the ballistocardiogram may be classified as grade 3; note absence of tachycardia.

The patient gave up smoking January 4, 1951, and after a few months improvement was striking; the attacks of angina occurring only after extended effort. On July 28, 1951, the blood pressure was 145/90. The electrocardiogram showed no change. *3.* The basal ballistocardiogram is now normal. *4.* After the exercise test, the ballistocardiogram is classified grade 1.

Case 6 (fig. 6); Myocardial Infarction; Smoking Sensitivity. B. K., male, 30 years of age, weighing 155 pounds. He had been complaining of angina pectoris since October, 1950. He was a heavy smoker. In May, 1951, the attacks of angina became more frequent and on June 30, 1951, he suffered an anterior myocardial infarction. After four weeks in bed, he has gradually increased his activities.

August 2, 1951. The blood pressure was 128/82. Physical examination and roentgenogram were normal; electrocardiogram shows evidence of a healed anterior myocardial infarction. *1.* Basal ballistocardiogram shows excellent myocardial recovery. *2.* After smoking a cigarette, tachycardia, decreases in the amplitude of all complexes, grade 1 respiratory variation and low HIJ waves are in evidence. *3.* Exercise test (eight trips) after the effects of the nicotine were permitted to wear off (30 minutes later); the ballistocardiogram is grade 1. This patient has been forbidden to smoke.

Summary

In detecting those subjects who have never adapted themselves to the toxic action of nicotine, the ballistocardiograph has proved to be a valuable instrument. The characteristic ballistocardiographic patterns that are obtained after smoking have been described. These patterns have been found in some smokers who were apparently without heart disease, as well as in cardiac subjects. However, the more marked ballistocardiographic abnormalities were recorded in patients with hypertension, coronary artery disease and neurocirculatory asthenia.

The clinical importance of determining nicotine sensitivity has been proved by the high incidence of subjective improvement in our patients with coronary artery and hypertensive heart disease, with positive smoking tests, after a period of tobacco abstention. Not infrequently, progressive improvement in the ballistocardiograms of those nicotine sensitive patients kept pace with their symptomatic relief.

It is our opinion that no patient with cardiac complaints, who shows a positive ballistocardiographic smoking test, should be permitted the use of tobacco.

Acknowledgment

The authors wish to express their appreciation to Dr. William Dock for his invaluable assistance in all phases of this study.

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The Low Frequency Velocity Measurement Ballistocardiograph

By J. E. SMITH, M.D. AND SAMUEL BRYAN, M.A.

The velocity measurement ballistocardiograph is described which has filter circuits to eliminate body tremor components. Small adjustable condensers are utilized on the input and output of the filter section to vary the frequency response of the circuit and thus create a sharper cut-off for occasional cases with high amplitude body tremor. The input and output condenser values are not above 5 mfd. in either section. By utilizing this type of circuitry, the lack of wave distortion makes it feasible to measure the ratios of wave amplitudes. The timing device makes it practical to time wave segments from the peak of the R wave, and a single channel recorder can be utilized. Normal standards are described and deviations from normal in coronary artery disease are discussed. The low frequency, velocity measurement ballistocardiograph is easily adaptable for routine office use.

FOR MANY years the ballistocardiograph has interested physiologists and research clinicians. The physiologic evaluation of the heart by recording mechanical heart actions which are imparted to the body is an approach made available through the use of the ballistocardiograph. This instrument thus affords a physiologic approach to many types of heart disease and seems to have a great prognostic value.[1]

In the past, different types of ballistocardiographs have been used. Starr[2] has been using a high frequency table and recording motions imparted to the table as a means of measuring forces of ballistic impact. Nickerson[3] has built a special table which can be critically damped and which has a low frequency of oscillation (1.5 cycles per second). Brown[4] has designed a table model with a high frequency oscillation similar to Starr's table, but with special electronic recording devices for simultaneous electrocardiograph and ballistocardiograph records on separate channels. Dock[5] has published technics of recording ballistocardiograph waves that utilize direct body pickups without the use of special ballistic tables. He first utilized the principle of the glycerine capsule placed against the head, later changing to the photoelectric cell in which the ballistic impact altered the amount of light source to the cell, and still later to a coil and magnet device which was placed directly on the body just below the knees. The coil was allowed to move with the body, and the magnet was held in such a way that it could not move; thus a difference of electric potential was created which could be measured on a string galvanometer.

Most of the electrical devices applied directly to the body have been displacement measuring devices. The most common and generally used is the photoelectric cell which is now available commercially. Strain gages have been advocated, and these are also displacement measuring devices. The coil and magnet principle, however, is a velocity measuring device, and the wave amplitude is based on the rate of displacement.

The measurement of the velocity of body motion shows only slight effect from respiration since the velocity of diaphragmatic motion is so slight (although actual displacement of the body is high enough to interfere with displacement recordings). The amplitude of the velocity ballistic wave is lower in expiration normally and correlates with Starling's law as venous filling of the heart during expiration is decreased. In patients with arrhythmias, the velocity waves following a long compensatory pause are always of greater amplitude, apparently due to the increase in diastolic filling. This again shows correlation with Starling's law.

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Instrumentation

The magnet and coil device is an electrical signal generator in which the signal generated is proportional to the relative velocity between the two. It is inherently capable of wide range frequency response since it is not used as a seismic or ballistic device.

The magnet is suspended by means of a compliant pivot (razor blades) from the stand which houses the coil. (See fig. 1.) Comparative records were taken to determine the effect of this type of support for the magnet upon the ballistocardiograph tracing compared with the

Fig. 1. The low frequency, velocity measurement ballistocardiograph is shown with the vertical steel rod that holds the magnet.

tracings obtained when the magnet was independently supported. Since no noticeable differences were obtained, the effect of the compliant mounting was therefore considered to be insignificant.

A series of tests was then undertaken to validate the velocity characteristic of the ballistocardiograph. It should be noted that the nature of the ballistocardiograph is affected by the associated equipment and the recording apparatus as well as by external vibrations originating in the building or personnel in the vicinity.

It was decided to determine the response of the system (coil-network filters-recorder) by injecting test signals from a suitable low frequency oscillator (Krohn-Hite or Hewlett-Packard) by means of a low impedance input in series with the pick-up coil. The output of the ballistocardiograph was then recorded on a Sanborn Viso-cardiette. By using selected frequency intervals and adjusting the input signal to a constant amplitude the response of the system was then traced on the recorder.

It should be noted that no attempt has been made as yet to determine the absolute velocity of the human body in this study. It is felt that this information is of academic interest only, since any device used would require extensive and laborious calibration procedures, and in the case of electronic devices be subject to line voltage variations, magnet strength, and other factors. As a matter of research interest, information on absolute velocities and displacements of the body due to the heart pulse should be undertaken.

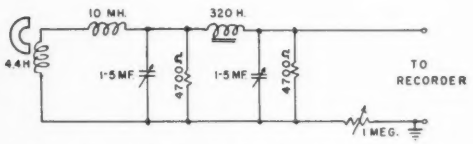

Fig. 2. Circuit diagram of the low frequency, velocity measurement ballistocardiograph.

The intrinsic value of the ballistocardiograph lies in the pattern of the tracing. Absolute amplitudes of velocities would be difficult to correlate, so we have used wave ratios and timing of waves as means of extracting significant data from the tracings. Thus, tracings of variable amplitudes for whatever reason may be directly compared.

Filters whose effect may be varied were built into this ballistocardiograph to eliminate the higher frequency signals not believed to be originating in the heart pulse. These high frequency components may be due to various factors such as 60 cycle hum picked up from the power mains, body tremors, ambient building vibrations, and other extraneous sources (See circuit diagram, fig. 2.).

Previous experience has indicated that the region of 2 to 8 cycles per second would cover most of the fundamental frequencies of body motion, and therefore the filtering was designed to have minimal effect in this region

while strongly attenuating frequencies above this range.

It can be seen from the calibration curves (fig. 3) on this model ballistocardiograph that the frequency response holds up quite well to about 8 cycles per second with the 2 microfarad (mfd.) output condenser and gives a reasonably flat response to about 6 cycles per second with the rapid roll-off filter (3 mfd. output; 5 mfd. input).*

When the frequency response of a system shows a decreasing response at the rate of 6 decibels (one-half) per octave of frequency increase, then a velocity pickup will yield a

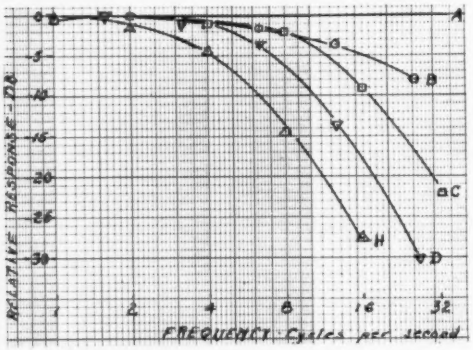

FIG. 3. Frequency response curves. A: Coil and magnet, no filter. The coil has constant signal output to 200 cycles. B: Choke filter; no condensers in the circuit. C: 2 mfd. output condenser only. D: 3 mfd. output condenser and 5 mfd. input condenser. H: Shows frequency response with 10 mfd. output and 10 mfd. input condensers.

displacement signal. Investigators using velocity pickups are cautioned to determine the frequency response of their recording system to ascertain the nature of the tracing (velocity, displacement or partially integrated). A velocity recording has different characteristics from a displacement recording, and therefore tracings should be validated as either velocity or displacement recordings for comparison purposes. Intermediate tracings should be compared by means of frequency response characteristics rather than using signal lags and timing as a basis of estimating the amount of integration.

A velocity recording of a given harmonic motion differs from a displacement recording basically in that the peak of the velocity wave precedes the peak of the displacement wave by 90 degrees. Further, where the motion is complex, the higher frequencies receive greater relative amplification when studied as velocities and thereby reveal events which might be obscured in displacement recordings. However, the problem of suppression of high frequency ambients becomes more demanding in velocity recording; hence, the need for adequate filters. (Compare *A* and *D* in figure 5.)

Timing of the peaks of ballistic waves is affected by the following: (a) the nature of the recording—velocity, displacement or intermediate; (b) time delay in the filter or associated equipment; (c) time lag of the timing reference signal in relation to ballistic waves, for example, carotid pulse.

For comparison purposes, it must be noted that any filter, attenuating within the frequency range of body tremor, will probably cause some signal delay. Thus the filter demonstrated in figure 3 using no condenser (frequency response curve B) has a signal lag of .01 to K wave peak when compared with a coil and magnet with no filter. The frequency response curve shown in figure 3, using a 2 mfd. output condenser (curve C), has a signal lag of .02 second to K peak. The rapid roll-off filter using 3 mfd. output, 5 mfd. input condensers (frequency response curve D) has an average time lag of .03 to H and I peaks and .04 to J and K peaks. The timing relationship of velocity and displacement is shown in figure 4.

It should be noted that the basic curve outline is not changed by filters when compared with the curve obtained with the coil and magnet. In our experience the timing of our 2 mfd. filter is very close to the Starr type of high frequency ballistic table. Also, the rapid roll-off filter (3 and 5 mfd.) has timing nearly identical with the displacement ballistocardiograph without the filter (fig. 4*D*). In spite of the timing similarity obtained from

* Circuit analyses and frequency response studies were done by Mr. Irving Levine, electronic scientist, Sound Section, U. S. Bureau of Standards.

displacement records and from the velocity recording made in conjunction with the 3 and 5 mfd. filter combination, the two do not yield recordings of the same character. The 3 and 5 mfd. filter used with a velocity pickup gives a velocity recording which is attenuated starting at a frequency of about 5 cycles per second.

It should be noted that in many normal individuals it is possible to obtain an excellent velocity ballistocardiograph with only a coil and magnet in the absence of external ambient vibration interference. This can be seen readily in figure 4*A*. However, in most cases of coronary heart disease it is nearly impossible to

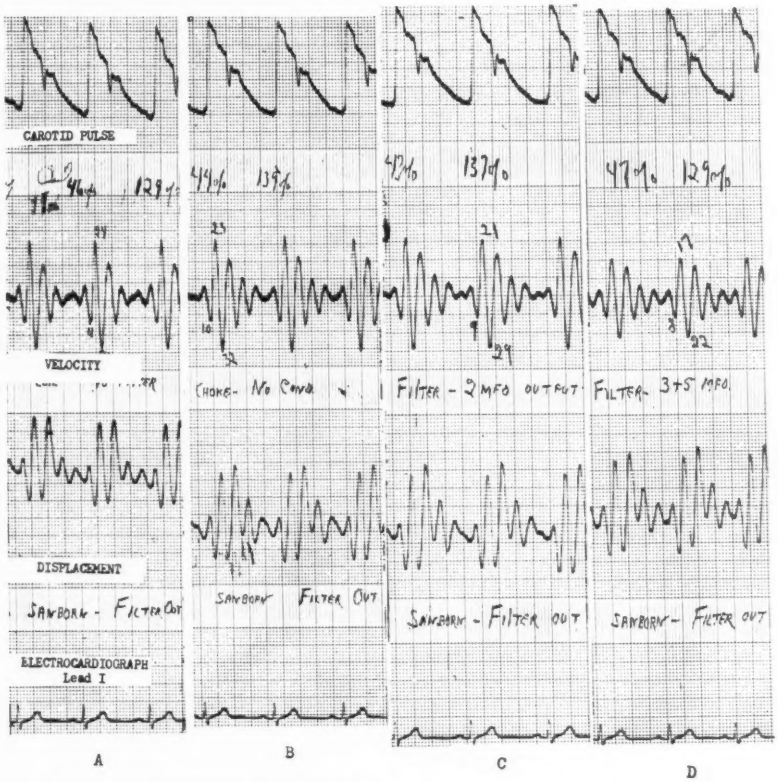

FIG. 4. Simultaneous tracings of velocity and displacement to show timing relationship and phase shift. These are taken on a Sanborn Poly Viso at a paper speed of 25 mm. per second. The carotid pulse has a .02 second lag from tubing. The velocity curves of *A*, *B*, *C*, and *D* are made with frequency response curves of A, B, C, and D of figure 3.

The fundamental frequencies of body motion if of a frequency lower than 5 cycles will be velocity tracings, and above 5 cycles will be partially integrated into intermediate velocity-displacement recordings. This technic does yield useful clinical information in that the velocity characteristic of the body motion is substantially retained while strongly filtering body tremors and other extraneous signals.

obtain useful velocity ballistocardiograms from a coil and magnet only, as signal (or velocity) is of lower amplitude, and the signal-noise ratio becomes larger (ratio of body tremors to signal). Also, the higher the frequency amplitude response of the recorder, the more susceptible the recording becomes to ambient vibrations. This effect is more noticeable in recordings of patients with coronary disease.

Ambient Vibration Interference

In the use of velocity measurement pickups, a phenomenon which we have labeled ambient vibration interference must be understood before clinical measurements can be utilized. We have utilized the term *ambient vibration interference* because of the similar problem in sound engineering utilizing similar electrical apparatus. The sound engineers call this *ambient noise interference* and except for differences in the frequency range, the problem is similar.

The literature that has been published to date shows convincing evidence that this phenomenon is not understood by clinicians and explains to a great extent why some investigators have been unhappy about the various electromagnet devices used for velocity measurement.

Ambient vibration interference usually has its origin in two sources. (1) The most important source is the table on which the patient and instruments rest. It is difficult to use any wooden table that is not fixed to the walls and the floor for measurements of body velocity. Since either the magnet or coil is fixed to the table, any table movement distorts the body velocity waves. The actual motion of the table is slight, but due to the high velocity of displacement and the sensitivity of the pickup, the amplitude of ambient interference may be appreciable. In ballistic curves of young normal individuals the main distortion occurs in the H wave and variations in the HI segment in relation to the IJ segment. This will also produce great variations in the amplitude of the L wave. In the main, however, ambient vibration interference is not easily recognized because of the wide amplitude of the IJK complexes. In the older ages where velocity is lower in normal people, the ambient vibration interference is more serious and may completely distort the record. (2) The other source of ambient vibration interference is in the building structure in which the table is resting. In general, if the building is of reinforced concrete construction, there will be little interference. However, in many older buildings, especially with wooden beam supports and wooden floors, people walking in adjacent rooms and corridors will produce changes in velocity waves; and we have seen distortion produced by people standing next to the recording table that seems to be from transmitted vertical forces from heart beats into the floor.

Once an investigator is conscious of the effect of ambient vibration interference, the problem is simple to test for. (1) To test for building interference, place the instrument, partially supported on a pillow, on the ballistic table, and support the magnet in the usual manner. Start up the recording machine and walk around the room and the table. Any deflection of the baseline is due to vibration from the building transmitted into the table. Under ideal conditions there should be no deflection of the recorder even if people jump up and down in the room. (2) To test for ambient vibration interference from the table, place the patient on the table and fix the instrument so that the magnet is deflected by the table instead of the patient. If there is any motion in the table or a deflection of the baseline under these circumstances, then ambient vibration interference is coming from the table and may produce some distortion on the velocity record. In general, ballistic velocity curves taken with the patient on the floor of a reinforced concrete building will show no evidence of such interference.

In figure 5, tracings are shown to illustrate the amplitudes of ambient vibration interference as related to frequency response. These tracings are made on the same person while resting on an ordinary commercial wooden treatment table. The building structure is wood frame and of temporary construction. During the time that these tracings were recorded, a water cooling system was running in the next room. *A* was recorded with a coil and magnet pickup with no filter. The ambient interference is of such amplitude that the primary velocity record is impossible to interpret. *B*, *C*, and *D* are recorded on frequency response curves *B*, *C*, and *D* of figure 3. The interference vibrations in *D* look similar to some illustrations that have recently been published.

Timing of Ballistic Waves

With the velocity measurement type of ballistocardiograph, the phonocardiographic pick-up recorded simultaneously with the ballistocardiograph is generally adequate as a basis of timing. This is especially true in timing the diastolic phases of the cardiac cycle as the second heart sound is based on mechanical changes and is much better for diastolic timing than the electrocardiograph. However, in many cases of valvular disease the heart sounds are inadequate for timing purposes.

The QRS wave of the electrocardiograph fortunately falls in a period of low electrical potentials when the ballistic waves are recorded and precedes the nadir of the I wave by an average of .12 to .16 second and precedes the H wave deflection by .05 to .09 second. The QRS then could be recorded theoretically on the same string at this point.

It seems that the ideal method is one that would enable us to increase the QRS potentials of the electrocardiograph and decrease the ballistocardiograph potentials at the same time. In difficult cases the pure ballistic waves could be decreased in amplitude while the QRS was increased in amplitude. By a method of this type we could use lead II of the electrocardiograph and dampen the amplitude of ballistic waves as necessary for timing purposes. Using any standard lead as a method of timing has a distinct advantage over chest leads. The heart sound recorder is placed over the apex, and it is difficult to use chest electrodes at the same time in the same area. In this way an accurate method of timing could be devised to fit all cases and still use only a single channel electrocardiograph machine.

This problem was solved in the following manner. A 1 megohm potentiometer was inserted in the ground lead of the ballistocardiograph (negative lead). (See fig. 2.) It was found that 1 megohm was sufficiently high to remove the ballistic signal from the electrocardiograph circuit and record the electrocardiograph only. By decreasing the resistance, it is possible gradually to increase the amplitude in the ballistocardiograph and decrease the amplitude of the electrocardiograph. As the resistance is decreased, the QRS is decreased and correspondingly the ballistic impact waves are increased in amplitude. This enables us to vary the amplitude of the QRS and ballistic

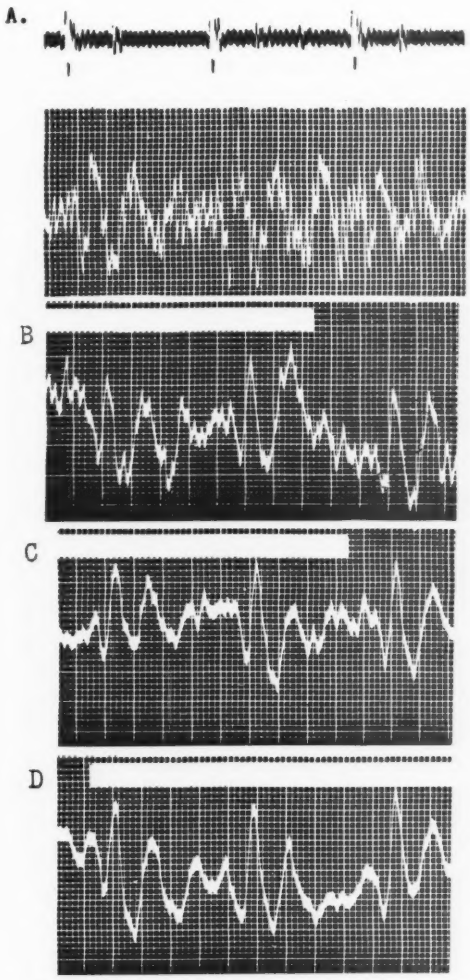

Fig. 5. This shows the effect of ambient vibration interference when related to frequency response. *A*, *B*, *C* and *D* represent tracings taken with frequency response A, B, C and D of figure 3.

waves as desired, and this timing method can be adapted to any ballistic wave regardless of amplitude or contour. Figure 6 shows the ballistocardiograph and electrocardiograph recorded simultaneously.

The Normal Velocity Ballisto-cardiograph Wave

As in Starr's original designation of the ballistic waves, the first deviation from the baseline is designated as the H wave, which is considered to be partly due to auricular systole and partly to the apex thrust of the heart. De Lalla[6] has described a footward deflection

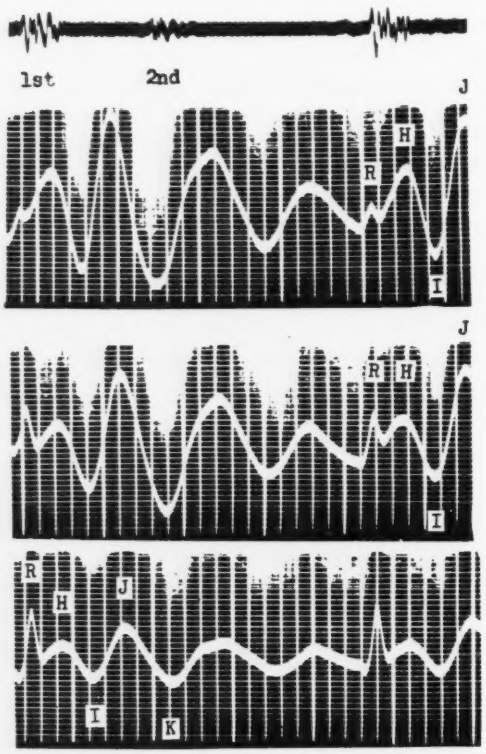

Fig. 6. Simultaneous record of the electrocardiograph and ballistocardiograph with changes in resistance from adjustment of the potentiometer.

that precedes the H wave and has labeled this the G valley. This has been seen frequently in patients with slow pulse rates. The G valley may be due to the deceleration in the ventricles of a footward traveling auricular impulse. The I wave is supposed to be caused by the footward recoil of the body due to ejection of blood from the ventricles. The J wave has been ascribed to the impact of blood flow on the aortic arch and pulmonary bifurcation. The K wave represents deceleration of blood in the aorta and smaller vessels.

The causes of the diastolic waves L, M, N, O, are more conjectural. Nickerson[7] believes the L wave to be due to a reflected wave of blood traveling up and then down the long column of the descending aorta. This may correspond to the reflection of blood from the closing of the pulmonary and aortic valves.

In the velocity measurement type of ballistocardiograph the ballistic afterwaves in normal people are nearly sinusoidal in character and may represent the natural decay of a vibrating body mass on its elastic tissue supports with each heart beat. This is probably true in normal people only to the extent of an "in phase" relationship to oscillating blood and body vibration. Actually, the ballistic afterwaves are related to real circulatory events and not to simple decay waves. In some of our cases of aortic insufficiency the L waves are of much greater amplitude than the J wave. In coarctation the L wave is much smaller than the N wave. Thus, the deep K in aortic insufficiency and the short K in coarctation are definitely related to changes in the afterwave pattern. Furthermore, in many cases of coronary disease the most prominent wave is an L wave.

In the development of normal standards of the velocity waves, 100 normal people between 20 and 30 years of age were examined; 75 were males, 25 were females. In this group, all had normal double two-step exercise tests as well as blood pressure readings below 150/90, and no clinical evidence of cardiac or pulmonary pathology.

The peak of the R wave was used as a time base. The time of occurrence of the H wave, I wave, J wave, and K wave was measured. These measurements are referred to as the R–H, R–I, R–J, and R–K intervals.

Also, the relative amplitudes of the segments H to I, I to J, and J to K, were measured. To do this the HI is expressed as percentage amplitude of the IJ, and the JK is expressed as a percentage amplitude of the IJ segment. This type of measurement stresses wave form rather

than absolute amplitude and follows the outline used by Jones and Goulder.[8]

The use of wave ratio measurements is clinically feasible and shows excellent percentage correlation among most normal adults. The use of absolute units for velocity measurement will undoubtedly be of clinical importance when instrumentation can be standardized and clinical technics thoroughly understood. At present, due to the diverse types of equipment and technics, absolute values of velocity measurement are purely theoretic. The clinician, however, will be able to compare amplitudes of velocity measuring devices from normal to abnormal; and thus by comparison he will be able to interpret low and high velocity of body motion. In studies done on the same patients at daily intervals, there is only slight variation in amplitudes made under the same environmental conditions. The magnet has a placement marker and, since the space relationship of the coil end magnet is fixed, relative amplitudes on the same person are quite similar. Even if wide variation in magnet placement should take place, with variation in amplitudes, the measurement of wave ratios rarely exceeds one standard deviation in repetitive studies. The timing has been constant for the same individual.

Standards for Velocity Ballistocardiograms

Normal Subjects. These standards are based on the findings in 100 normal people between the ages of 20 and 30 years. There were 75 males and 25 females.

(1) Timing:

	Males (75)		Females (25)	
	Mean	Standard Deviation	Mean	Standard Deviation
R-K	.30	.02	.27	.02
R-J	.21	.01	.19	.01
R-I	.14	.01	.13	.01
R-H	.08	.01	.07	.01

(2) Wave Ratio Measurements:

Males		Females	
Mean	Std. Deviation	Mean	Std. Deviation
Percentage HI of IJ			
52	6	47	4
Percentage JK of IJ			
128	8	133	9

Since it can be said that the measurements in the majority (95 per cent) of all normal subjects will fall within plus or minus 2 standard deviations, any observations falling close to or above 3 standard deviations from the mean should be carefully investigated before judgment of normality is made.

There were no detectable higher frequency components in the ballistic waves of these normals (above 8 cycles). Thus, whether measured with coil and magnet or filters, there was no notching of the HI, IJ, or JK segments. Occasional normals showed two distinct components of the H wave peak, however, and timing was made to the first peak.

Statistical evaluation reveals that these differences in timing are true differences (p is considerably less than .01 in all cases) and thus separate standards for males and females should be utilized.

The standards of wave ratio measurements and timing were made with respiration suspended during quiet respiration as near mid-inspiration as possible. During quiet respiration, there is a decrease in amplitude or velocity curves in expiration, and in most of our normal subjects the percentage relationship of each wave segment is maintained. In a few normal subjects, however, while breathing, some beats at maximal point of expiration lowered the IJ amplitude so that the HI segment was in slightly higher percentage. Even in these cases, the HI did not exceed 75 per cent of the IJ segment. Also, when the potentiometer is used for timing and the ballistic amplitude is decreased, the T wave exerts an influence on the H wave amplitude so that

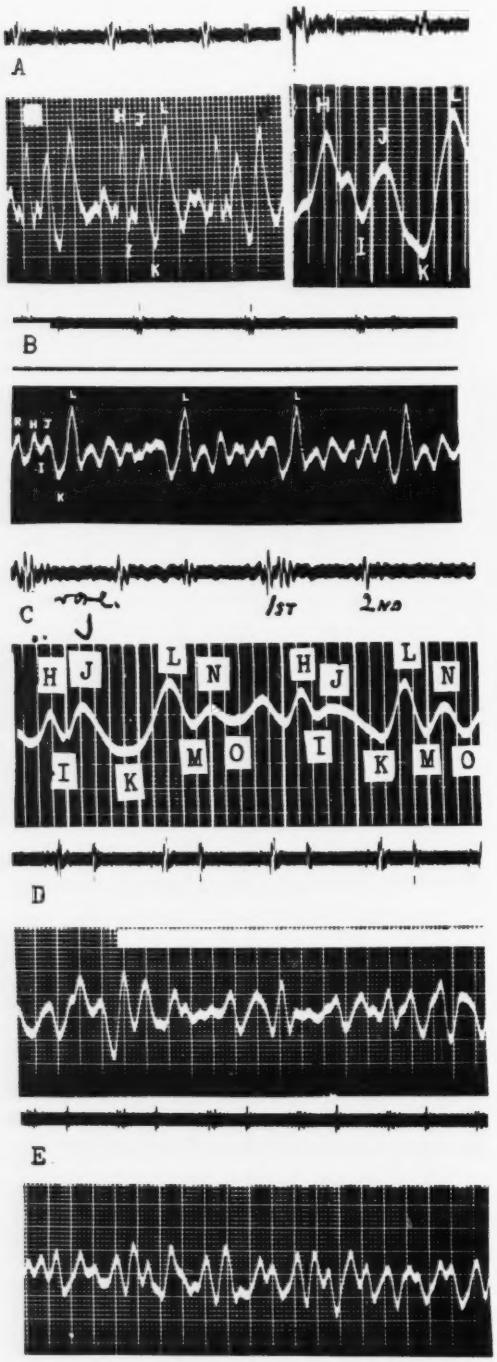

FIG. 7

there may be some time delay from R to H and change of percentage relationship between HI and IJ segments.

It must be realized that changes in these measurements may result from environmental ambient vibration interference (faulty technic) and electrical circuits that change the frequency response characteristics. These standards are based on a coil and magnet pick up with no filter for timing purposes and a filter

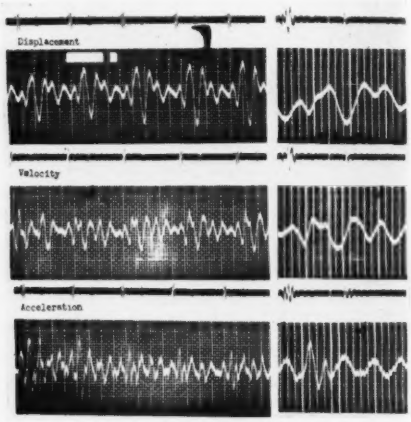

FIG. 8. Case of healed myocardial infarct. Electrocardiograph returned to normal following complete healing. The displacement curve looks normal, but the change in the IJ slope represents changes in velocity and acceleration that are readily seen. The fast paper speed (75 mm. per second) shows amplitude relationship and phase shift when displacement, velocity and acceleration are compared in relation to higher frequency components such as notched J waves. The displacement curve has been amplified twice normal to show abnormality of form.

using the 2 mfd. output condenser (frequency response *C* of fig. 3) for measuring of wave ratios. The 3 and 5 mfd. condenser (frequency response curve *D* of fig. 3) system should be used only as an auxiliary filter to measure wave ratios in the cases where body tremor components are of very high amplitude.

FIG. 7. The velocity waves from five persons with proved coronary artery disease. In *A*, double amplification is used with frequency response curve *E* of figure 3 to show high frequency notching. When the velocity ballistic waves were recorded, these cases were healed and ambulatory.

Patients with Coronary Artery Disease. In 50 cases of known coronary heart disease we have found no cases in which velocity measurements fell within these standards of normal, and the majority of the velocity curves were so completely changed that the various wave segments could not be identified with certainty. In this group of 50 patients we have selected only patients in which acute episodes of coronary occlusion with electrocardiograph confirmation had taken place. However, in patients with pulmonary diseases such as emphysema, the ballistocardiogram may deviate widely from these normal standards even though evidence of coronary artery disease is not present. There are five cases illustrated from this group of 50 cases in figure 7.

The finding of consistently abnormal ballistic curves in coronary disease is not in complete accord with the findings of other investigators who have been using displacement measuring devices.[9] Velocity is a more sensitive index of abnormality than is displacement due to the relative higher frequency. In figure 8 a tracing from a patient with healed myocardial infarction is shown. It should be noted that the displacement curve seems to be normal, but the velocity and acceleration curves look entirely different. The fast paper speed (75 mm. per second) shows the relationship. The slope change of the IJ segment on the displacement curve is difficult to see but represents a rather marked change in velocity and acceleration. The notching of the J wave is readily seen in velocity curves and is even more prominent on the acceleration curves.[10] This patient had typical history of myocardial infarct with electrocardiographic changes. After healing, the electrocardiogram returned to normal.

Summary and Conclusions

1. The low frequency, velocity measurement ballistocardiograph has been described.

2. The influence of ambient vibration interference on velocity measurements has been discussed, and the importance of this phenomenon has been emphasized.

3. The timing of ballistic waves has been discussed, and a simple device for the recording of the QRS of the electrocardiograph and the ballistocardiograph has been demonstrated.

4. Typical velocity curves have been demonstrated in normal subjects and in patients with coronary artery disease.

5. Normal standards for velocity waves have been described, based on the analysis of 100 normal people between the ages of 20 and 30 years.

6. The measurement of the velocity of body motion seems to have great clinical application, and the diagnostic value in coronary artery disease has been presented.

Addendum

Since the preparation of this paper Gubner has described a similar method of superimposing the R wave of the electrocardiographs and the ballistic wave for timing purposes. (Gubner, R.: Circulation **4:** 239, 1951).

Acknowledgment

The authors are indebted to John Magin, Electronic Engineer, Civil Aeronautics Administration, New York, New York, who collaborated on the electrical engineering features of this ballistocardiograph, and to the Sanborn Company for the loan of their photocell ballistocardiograph. The authors also acknowledge the assistance of the Psychology Branch, C.A.A., Washington, D. C., for their statistical analyses.

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Nutritional Factors in Hemodynamics

II. Hypertension during Pteroylglutamic Acid Administration in Albino Rats

By Richard E. Lee, M.D., Ph.D., Sachiko Tanaka, B.A., and Elizabeth A. Holze, B.A.

Albino rats treated with pteroylglutamic acid (PGA) developed a significant increase in blood pressure, as compared with litter mate controls of the same sex. The hypertension was associated with wedge-shaped fibroblastic renal cortical lesions. Factors possibly important etiologically in the elevation of blood pressure are discussed in relation to certain of the metabolic roles of pteroylglutamic acid.

AN INTERRELATIONSHIP between certain of the actions of ascorbic acid and of pteroylglutamic acid (PGA) has been reported recently by several laboratories. The "tyrosyluria" present in vitamin C deficient guinea pigs[1] can be abolished by the parenteral administration of pteroylglutamic acid, although the deficiency of vitamin C and the subsequent development of scurvy is not ameliorated.[2-4] Massive doses of this vitamin will similarly inhibit the anticipated "tyrosyluria" of scorbutic infants.[5] In addition, young monkeys on a synthetic diet devoid of pteroylglutamic acid and of ascorbic acid develop a megaloblastic anemia which responds either to pteroylglutamic acid or to ascorbic acid administration.[6]

It has been established previously that vitamin C has an important role in maintaining vasocompensatory processes in the peripheral circulation.[7, 8] The evidence outlined briefly above suggested that metabolic association of ascorbic acid and pteroylglutamic acid might conceivably extend into hemodynamic mechanisms. For this reason, studies have been initiated concerning blood pressure levels, tissue vitamin C concentrations and certain peripheral vascular reactions in animals fed synthetic diets with and without pteroylglutamic acid supplementation. It is the purpose of this report to describe a blood pressure elevation with renal lesions that accompanies administration of pteroylglutamic acid to albino rats.

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Methods

Twenty-seven albino rats of the strain developed in this laboratory were individually housed at age 21 days and fed a synthetic diet* devoid of pteroylglutamic acid. They were maintained on this diet for a total period of six weeks (to age 9 weeks). Seventeen were given intraperitoneal injections of a suspension of pteroylglutamic acid, 1.0 mg. per cc. distilled water per 100 Gm. body weight, three times weekly. The material was made up freshly immediately prior to each injection. The remaining 10 animals received no supplementation. After six weeks on this diet, 48 hours following the last dose of pteroylglutamic acid, the carotid blood pressure of each rat was recorded on a mercury manometer for a minimum period of six minutes. General anesthesia was provided by sodium pentobarbital, 3.5 mg. per 100 Gm. body weight. Blood pressures were similarly measured in 22 additional albino rats of the same strain receiving a regular laboratory pellet diet without additional pteroylglutamic acid. Observations on each animal receiving the injections were compared with those on litter mate controls of the

* The diet consisted of:

Supplemented Diet		*Supplements 1%* *Mg./100 Gm. diet*	
Casein	18%		
Lard	8%	Thiamine	0.8
Cornstarch	49%	Riboflavin	0.8
Sucrose	14%	Pyridoxine	0.8
Agar	2%	Pantothenate	1.5
Salt	4%	Nicotinic Acid	1.5
CLO	1%	Nicotinamide	1.5
WGO	2%	Choline Chloride	400
Salad Oil	1%	Inositol	100

same sex receiving either the synthetic diet or the laboratory pellet diet. Individuals were selected whose average daily food consumption and body weights were as nearly comparable as possible. At the end of the experimental period, the animals were sacrificed and sections of the kidneys were stained with hematoxylin and eosin for microscopic studies. Samples of liver, kidney and adrenal of animals from this series and from others similarly treated were assayed for ascorbic acid concentration using a modification of the method of Roe and Kuether.[9]

TABLE 1.—*Mean Blood Pressure in Each Group of Animals*

Animal Group	No. of animals for B.P. Determinations			Mean B.P. at 6 weeks (aged 9 wks.)		Standard Error (B.P.)
	Sex					
Synthetic Diet	Male	4	10	140	143	4.7
	Female	6		145		
Synthetic diet plus 1 mg. PGA/100 Gm. 3× weekly intraperitoneally	Male	8	17	168	172	5.04
	Female	9		175		
Stock Pellet diet	Male	14	22	145	145	2.88
	Female	8		145		

RESULTS

The blood pressures of the rats are recorded on table 1. After six weeks of treatment, the rats receiving pteroylglutamic acid had uniformly developed a significant hypertension (table 1). There were no differences in the blood pressures of the two control groups. The concentrations of ascorbic acid in the adrenal glands and in the kidneys were not influenced by the administration of pteroylglutamic acid. Liver vitamin C was considerably elevated in all rats on the synthetic diet; with moderately but not significantly greater amounts in livers of animals given pteroylglutamic acid (table 2). Also of interest were differences observed between the sexes with regard to tissue levels of ascorbic acid. This finding, not related to the increased blood pressure associated with injections of pteroylglutamic acid, is under further study.

Although the kidneys of treated rats were equal in weight to those of controls, the renal cortex surface in 15 of the 17 animals receiving pteroylglutamic acid was dotted with whitish, slightly contracted scars of from 0.5 to 2.0 mm. in diameter. These areas extended 1.0 to 3.0 mm. into the cortical parenchyma as small wedge-shaped lesions containing nu-

TABLE 2.—*Average Tissue Ascorbic Acid Concentration**

Animal Group	Number of Animals	Ascorbic Acid (μg./Gm.)		
		Kidney	*Liver*	*Adrenal*
Stock Pellet diet	26 (15 males, 11 females)	174 S.E.–9.6	270 S.E.–14.6	2881 S.E.–135.0
Synthetic diet	16 (9 males, 7 females)	159 S.E.–9.76	345 S.E.–24.3	3272 S.E.–149.3
Synthetic diet plus 1.0 mg. of PGA/100 Gm. body wt. 3× weekly, intraperitoneally	19 (9 males, 10 females)	149 S.E.–6.0	359 S.E.–9.7	2905 S.E.–87.0

* Statistical examination of these data reveals that the high concentration of liver ascorbic acid in the rats receiving PGA is not of significance when compared with either of the two control groups. There is no significance in the differences shown in adrenal or kidney vitamin C. Animals on the synthetic diet had a relatively low kidney ascorbic acid concentration, regardless of whether or not the animals received PGA.

merous fibroblasts. Cells of the proximal and distal convoluted tubules within and immediately adjacent to these regions were usually moderately shrunken, with pyknotic nuclei and eosinophilic cytoplasm. The remainder of the renal cortex and the medulla, despite the number and extent of cortical scars, compared favorably with that of the control animals. Sections of the kidneys from one rat treated with pteroylglutamic acid showed rare atrophic glomeruli, but the other animals failed to demonstrate this change. Occasional dilatation of the convoluted tubules bordering the scarred portions was observed in approximately 50 per cent of the animals, but casts in the renal tubules were not observed.

Discussion

The tubular damage observed in these animals generally agrees with that previously described by others in kidneys of guinea pigs[10] and rats[11] treated with pteroylglutamic acid. Numerous casts, largely of pteroylglutamic acid or derivatives, with resulting tubule dilatation, were prominent features of the renal pathology noted by others, but casts were not found in the kidney tubules in the present study. This conceivably results in part at least from the fact that the dose of pteroylglutamic acid employed was significantly lower than that employed by other workers,[10, 11] and the material was administered three times weekly rather than daily as was the custom in other surveys.[10, 11]

It has been reported that an acute and transient rise in blood pressure occurred immediately following a single intravenous injection of pteroylglutamic acid (5.0 to 100.0 mg. per kilogram) in cats, dogs and in one rabbit. Within 30 minutes, however, the "blood pressure was always normal."[11] This finding contrasts with the rise in blood pressure accompanying relatively long term intraperitoneal administration of pteroylglutamic acid to rats at low dosage levels, for in this latter instance pressures were recorded 48 hours after the last intraperitoneal injection. Moreover, renal lesions following single doses of pteroylglutamic acid were not described.[11]

The mechanism by which a significant hypertension is obtained in rats treated with pteroylglutamic acid is at present obscure. Its association with renal lesions possibly suggests a renal factor comparable to that brought about by interference with renal blood flow, as with renal artery clamps, perinephric packs, or renal ligation. An excess of dietary pteroylglutamic acid, however, is associated with a reduced activity of liver *d*-amino acid oxidase and xanthine oxidase in the chick,[12, 13] and diminished xanthine oxidase activity in the rat.[14] Liver choline oxidase in the rat may also be altered by an increase in dietary pteroylglutamic acid.[14] It is conceivable that large amounts of parenteral pteroylglutamic acid might similarly interfere with the activity of certain renal or other enzyme systems that normally may inactivate endogenous hypertensive factors, and in this manner induce a sustained blood pressure elevation. Another possible explanation of the hypertension is suggested by recent demonstrations that pteroylglutamic acid is imminently concerned in transmethylation and the synthesis of choline and methionine.[15-18] In addition, under certain specific experimental conditions, the administration of pteroylglutamic acid accelerates methylation of a toxic substance and results in a consequent loss of available methyl groups from the body.[19] In these circumstances, the development of a yellow, fat-infiltrated liver and a reduced growth rate suggests a choline deficiency. This possible *antilipotrophic* nature of pteroylglutamic acid under induced conditions is of interest. In the present study, pteroylglutamic acid may have accelerated transmethylation in the body to a degree sufficient to induce a significant over-all deficiency of accessible methyl groups. The onset of hypertension subsequent to a brief transient period of choline deficiency in early life is well established in rats.[20-22] By producing a relative insufficiency of choline, or other methyl donator substances, administration of pteroylglutamic acid may result in hypertension perhaps by a metabolic action less direct than specific enzyme inhibition.

Summary and Conclusions

1. Blood pressure levels and tissue vitamin C concentrations have been determined in rats of our laboratory strain treated with pteroylglutamic acid (PGA).

2. Administration of pteroylglutamic acid for six weeks was accompanied by a significant blood pressure elevation.

3. In comparison with the control animals, the treated animals showed no differences in kidney weight or in the concentration of ascorbic acid in the kidney, liver and adrenal gland. Injections of pteroylglutamic acid were associated with numerous wedge-shaped fibroblastic lesions of the renal cortex.

4. The possible mechanisms by which excess pteroylglutamic acid might produce hypertension are discussed in relation to the metabolic roles of the vitamin.

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The Water and Electrolyte Content of the Human Heart in Congestive Heart Failure with and without Digitalization

By NORMAN E. CLARKE, M. D., AND ROBERT E. MOSHER, PH.D.

The hearts of 25 patients have been serially analyzed for water, chloride, sodium and potassium content. Sixteen hearts were of patients who died in circulatory heart failure; some received digitalis and some did not. The water content of all hearts was the same. In circulatory heart failure, the sodium increases and potassium decreases but the sum of the two remains the same as in normal hearts, indicating a reciprocal relationship. Digitalis in circulatory heart failure restores the alkali metal values and ratios of heart muscle to near normal levels. Digitalis exerts a direct chemical action on the heart muscle.

THE ONSET and severity of congestive heart failure does not always conform to the objective evidence of heart damage, just as the anatomic findings in all instances do not correlate with the functional status of the heart. Therefore, one must suspect that congestive heart failure may result from either physical or chemical change in myocardial tissue, although critical chemical changes within the living heart muscle cell cannot be evaluated by present methods. According to Herrman,[1] the creatinine content of heart muscle is reduced in congestive heart failure and is partially restored by digitalis therapy. It appeared possible that digitalis might influence other constituents of the failing heart muscle, and the action of this drug in heart failure be due in part to its effect on the chemical balances existing in the heart tissue. We have investigated this possibility by studying the chemical topography of the human heart. The particular components studied were sodium, potassium, chloride and water content.

METHODOLOGY

Sampling. An effort was made to secure samples as soon after the time of death as possible, the average elapsed time from death to autopsy being eight hours. Samples approximately 20 Gm. in size were taken from the following five areas of hearts at autopsy: right auricle, midzone of right ventricle, midzone of ventricular septum, base of left ventricle and apex of the left ventricle. These samples were wiped dry of surface fluids and immediately subjected to analysis. All samples analyzed were trimmed so as to remove all visible fat and were carefully blotted before weighing to remove excess surface moisture.

Water Content of Tissue. Approximately 0.5 Gm. of tissue in thin slices was placed in a weighed aluminum dish and the dish reweighed. The difference in weight was taken to be the weight of the sample. The dish was then placed in an electric-air oven at 135 C. until it reached constant weight. The usual time required was two hours. The sample was then removed from the oven, cooled in a desiccator and reweighed. The loss in weight was taken to be the weight of water contained in the sample and calculations of per cent water content were made on this basis. This is essentially the method recommended by the Association of Agricultural Chemists for the determination of the water content of animal tissue.[2]

Chloride Content of Tissue. A 0.500 Gm. sample of carefully trimmed tissue was carefully weighed and transferred to a 125 ml. Erlenmeyer flask, 5 ml. of five normal sodium hydroxide solution and 20 ml. of distilled water were added and the sample was heated gently on an electric hot plate until solution was complete. The solution was cooled and approximately 20 ml. of distilled water, 7 ml. of concentrated nitric acid and then exactly 5.0 ml. of 0.01 normal silver nitrate solution was added and boiled gently until the silver chloride was completely coagulated and the solution was light yellow in color (10 to 15 minutes). The solution was cooled and 1 ml. of nitrobenzene added and shaken until the supernatant liquid was relatively clear. Two ml. of saturated ferric alum solution was added and titrated with 0.01 normal potassium thiocyanate to a *faint* pink endpoint. We found it advisable to run a reagent blank and to standardize the thiocyanate solution against the silver nitrate. The per cent

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chloride was computed according to the following formula:

$$\%Cl = \frac{(V_{AgNO_3} \times N_{AgNO_3} - V_{KCNS} \times N_{KCNS}) \times 0.0355 \times 100}{\text{Weight of sample in Gm.}}$$

Sodium and Potassium Content of Tissue. A 0.300 Gm. sample of tissue was carefully weighed and transferred to a 50 ml. Erlenmeyer flask. Five ml. of concentrated nitric acid and 5 drops of 70 per cent perchloric acid were added and then slowly evaporated to incipient dryness on an electric hot plate in a hood. No charring should occur. If the sample did char, 5 ml. of concentrated nitric acid were added and the sample was evaporated to dryness once again. It has been found that 5 μg. of vanadium as ammonium vanadate will accelerate this wet ashing procedure. After the sample reached dryness, it was cooled and 10 ml. of distilled water and one drop of concentrated hydrochloric acid added and warmed until all salts were in solution. It was cooled and transferred quantitatively to a 25 ml. volumetric flask and diluted to the mark with distilled water then mixed thoroughly by inversion. Then 1.0, 2.0, and 3.0 ml. aliquots of the standard solution were treated in the same manner as the tissue sample. Standards and unknowns were compared using the Beckman flame photometer. This technic is described by Mosher and co-workers.[3]

TABLE 1.—*Average Composition of Heart Muscle (per cent Composition of Wet Tissue)*

	H_2O	Cl	Na	K
A. Normals (7 Hearts)				
Right Auricle	81.2	0.15	0.120	0.139
Right Ventricle	80.7	0.14	0.112	0.196
Septum	79.2	0.12	0.094	0.309
Base Lt. Vent.	78.9	0.12	0.092	0.316
Apex Lt. Vent.	79.4	0.12	0.089	0.311
B. Cardiacs (11 Hearts)				
Right Auricle	78.8	0.16	0.138	0.120
Right Ventricle	79.0	0.15	0.139	0.179
Septum	79.7	0.15	0.130	0.239
Base Lt. Vent.	79.1	0.16	0.131	0.224
Apex Lt. Vent.	80.1	0.14	0.128	0.217
C. Digitalized Cardiacs (5 Hearts)				
Right Auricle	82.1	0.16	0.139	0.130
Right Ventricle	80.0	0.13	0.104	0.226
Septum	79.3	0.14	0.104	0.285
Base Lt. Vent.	79.5	0.13	0.096	0.290
Apex Lt. Vent.	79.6	0.14	0.105	0.284

One liter of the stock standard solution contained 0.255 Gm. of sodium, 0.625 Gm. of potassium, 0.0168 Gm. of magnesium, and 0.310 Gm. of phosphorus. The weighing forms were: sodium and potassium as chlorides, magnesium as distilled magnesium metal, and phosphorus as diammonium hydrogen phosphate.

A total of 50 human hearts were analyzed, using the above technics. The data obtained from 23 of these hearts is presented. Of this group, 16 were patients who died in Providence Hospital with the clinical diagnosis of congestive heart failure. This study was to correlate special chemical changes in the myocardium with this clinical diagnosis. The criteria for selection of these hearts included the presence of severe congestive heart failure, the absence of obvious renal insufficiency and confirmation of heart disease as the chief cause of the congestive heart failure by postmortem examination. The etiologic diagnosis, confirmed by necropsy, was rheumatic heart disease in five, coronary heart disease in four, ancient coronary infarction in three and hypertensive heart disease in four patients. Five of these patients had received digitalis and 11 had not. All of the digitalized patients had received preliminary digitalization and been maintained on daily maintainance dosage of the drug. The hearts of seven patients were normal from both clinical and autopsy examination.

Since some variation in water content occurs in different hearts and in different areas of the same heart, it is advisable to express concentrations of elements on a dry tissue basis. Routine fat determinations were not made and we have calculated ratios of potassium to sodium to eliminate the effect of the fat content of trimmed heart tissue which we have found by analysis to be normally 1 to 3 per cent. It is impossible to be sure of fat content, as present methods must show ether or other solvent extractables which may not represent solely fatty or lipid materials. Likewise, as collagen tissue comprises only 0.7 per cent of heart substance,[4] it causes no major error in this data. These analyses, therefore, should be characteristic of heart muscle and its immediate fluid environment.

RESULTS

As presented in table 1, the water content of the normal auricle is 81.2 per cent and the septum, base and apex of the left ventricle average about 79 per cent or the lowest water content, while the 80.7 per cent value for the right ventricle stands intermediate to the right auricle and left ventricle. There is a slight difference in the left ventricular water content of normal, diseased or digitalized diseased hearts, while that of the right auricle of cardiac

patients drops to 78.8 per cent. These variations in water content are not great enough to hold any significance.

When digitalis has been given, the auricular muscle chloride is 0.15 per cent and the lowest chloride content is 0.12 per cent in the septum, base and apex of the left ventricle. The sodium is highest or 0.12 per cent and potassium lowest or 0.139 per cent in the auricle but the reverse is true of these elements in the left ventricle where they appear to be distributed uniformly, with sodium at approximately 0.092 per cent and potassium at 0.312 per cent. In congestive heart failure the same relative relationship of the auricle and ventricle with respect to sodium and potassium persists but, in general, sodium increases and potassium decreases in all sections of the heart. When digitalis had been given for the congestive heart failure, there was a definite reversal of the electrolyte pattern toward normal levels. In all analyses the right ventricle figures stand intermediate to the auricular and left ventricular findings.

The effect of digitalis on the heart muscle electrolytes in congestive heart failure is illustrated by figure 1. This represents heart sections from the left ventricle only, with the figures for the ratio of potassium to sodium in milliequivalents on the abscissa and the number of samples of normal, diseased and digitalized diseased hearts on the ordinate. The samples from normal hearts fall between the ratios of 1.25 and 2.50, and for hearts of cardiac patients between 0.25 and 2.00. The sections from diseased hearts which had been digitalized all lie closer to normal values than they do to the values for undigitalized diseased hearts, although there is a certain amount of overlap. Apparently digitalis acts on the heart muscle in congestive failure so as to restore the cellular electrolytes (sodium and potassium) to within normal ratios.

To determine whether there was a change in the total amount of electrolytes in the failing heart, computation was made of the total milliequivalents of chloride and of the alkali metals per 100 Gm. of dried heart tissue. As presented in table 2, the normal left ventricular chloride level of 16 mEq. increases to 21 mEq. in the left ventricle muscle of undigitalized cardiac patients, but remains at 21 and 20 mEq. in the right auricle and right ventricle, respectively, of normal and diseased hearts. The sodium increases and potassium decreases in all muscle sections of the cardiac patients, but the total milliequivalents of sodium and potassium in the various muscle sections of the cardiac patients remain about the same as in the corresponding sections of the normal hearts, except that the right auricle decreases to 42.8

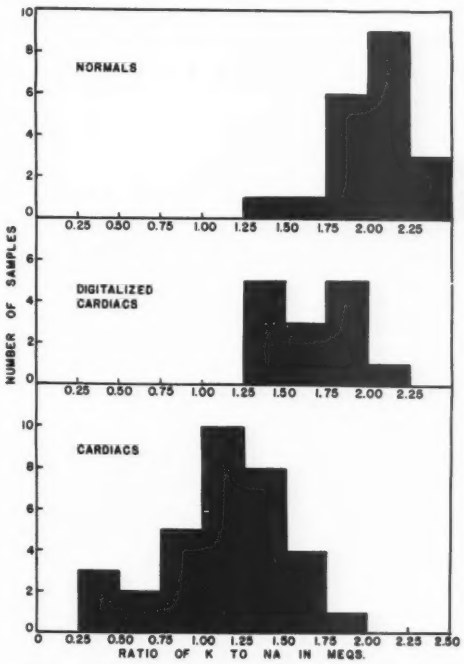

FIG. 1. The effect of digitalis on the potassium-sodium ratio of the left ventricular heart muscle in circulatory heart failure.

mEq., the normal being 47.8 mEq. Due to the natural variability of the auricle, it is doubtful if this difference has any statistical significance. The potassium-sodium ratios on the basis of milliequivalents also increase progressively from the right auricle to the left ventricle. The hearts of digitalized cardiac patients show lower chloride and sodium and higher potassium values than do the hearts of undigitalized cardiac patients. The total milliequivalents of sodium and potassium of all heart muscle sections in the digitalized cardiac pa-

tients are about equal to those for normal hearts except for a greater than normal increase in the right auricle. It is significant that in contrast to the great change in potassium-sodium ratios between the normal and diseased heart, the total number of milliequivalents of alkali metals in 100 Gm. of dry heart tissue is essentially the same in all corresponding heart sections of both groups.

In table 2, average deviations are given for normal hearts and for hearts from patients

electrolyte balance in a heart. In diseased hearts the deviations for the left ventricular samples are the same as or greater than those for samples from the right auricle or right ventricle. This condition does not occur with normal or digitalized diseased hearts.

To establish that there is a relationship between potassium and sodium, as suggested by the fact that there may be wide variation in potassium-sodium ratio between samples having the same combined amounts of these el-

TABLE 2.—*Milliequivalents of Chloride and Alkali Metals per 100 Gm. of Dried Heart Tissue with Average Deviations of Analysis.*

	Cl	A.D.*	Na	A.D.*	K	A.D.*	Na-K	A.D.*	K/Na	A.D.*
A. Normals (7 Hearts)										
Right Auricle	21	± 4.3	27.5	± 4.5	20.3	± 8.2	47.8	± 9.0	0.74	± 0.31
Right Ventricle	20	± 3.6	25.6	± 4.1	26.1	± 3.6	51.7	± 5.6	1.02	± 0.29
Septum	18	± 2.5	19.6	± 2.2	38.1	± 3.2	55.7	± 2.9	1.94	± 0.30
Base Lt. Vent.	16	± 1.1	19.1	± 1.2	38.6	± 2.6	57.7	± 3.2	2.02	± 0.10
Apex Lt. Vent.	16	± 1.5	18.5	± 1.6	38.1	± 2.6	56.6	± 4.2	2.06	± 0.13
B. Cardiacs (11 Hearts)										
Right Auricle	21	± 4.7	28.3	± 7.7	14.5	± 5.1	42.8	± 12.1	0.50	± 0.18
Right Ventricle	20	± 2.6	28.8	± 4.7	21.8	± 4.7	50.6	± 7.6	0.76	± 0.18
Septum	21	± 3.2	27.8	± 8.9	29.9	± 5.9	57.7	± 6.5	1.08	± 0.42
Base Lt. Vent.	22	± 3.3	27.2	± 5.3	27.4	± 6.4	54.6	± 6.0	1.00	± 0.29
Apex Lt. Vent.	20	± 3.4	28.0	± 4.4	27.9	± 7.9	55.9	± 3.0	1.00	± 0.32
C. Digitalized Cardiacs (5 Hearts)										
Right Auricle	28	± 6.0	32.1	± 7.2	20.0	± 2.9	52.1	± 6.1	0.58	± 0.22
Right Ventricle	18	± 2.0	21.5	± 2.7	29.1	± 6.2	50.6	± 6.7	1.38	± 0.32
Septum	19	± 1.0	22.4	± 2.5	35.1	± 1.5	57.5	± 3.3	1.57	± 0.15
Base Lt. Vent.	18	± 1.2	20.4	± 2.0	36.1	± 2.1	56.5	± 2.5	1.77	± 0.19
Apex Lt. Vent.	19	± 1.6	22.4	± 2.8	35.6	± 2.3	58.0	± 3.1	1.63	± 0.29

* Average deviations of analysis.

dying in congestive heart failure who had or had not received digitalis. In general, the deviations for hearts of undigitalized cardiac patients are greater than the corresponding values for the other two categories. Generally, the deviations for the right auricle and right ventricle are greater than those for the left ventricle. Computed percentage-wise, the deviations of potassium-sodium ratios are smaller than for sodium and potassium individually. This would indicate that the ratio is more reliable than individual sodium or potassium values as an index or criterion of the status of

ments, we have related these data statistically. We show in figure 2 a graph of the milliequivalents of potassium per 100 Gm. of dried heart tissue against the milliequivalents of sodium per 100 Gm. of dried heart tissue and have drawn an average line. Each point represents the data obtained from one sample of left ventricular tissue. The correlation coefficient for this data is -0.67. A correlation coefficient of 0 would show that there is only a random scatter of points, while a value of plus or minus 1 would indicate perfect correlation and all points would lie on one straight line. Since the

value for our data is −0.67, we can conclude that there is a high probability of correlation between sodium and potassium levels in tissue, probably in the nature of some type of equilibrium.

The limits of variation of alkali metals in the right auricle, right ventricle and left ventricle are presented in figure 3. The sum total of milliequivalents of sodium and potassium per 100 Gm. of dried heart tissue was used, since this value was found to be fairly constant for both normal and diseased hearts. The values are from normal, diseased and digitalized diseased hearts. The greatest variation occurs in the auricle where the values range between 20 and 80, or a range of 60, while the least variation occurs in the left ventricle with a range between 40 and 70, or a variation of only 30. The right ventricle once again stands intermediate with a variation from 25 to 75, or a range of 50. The great difference in the total milliequivalents of alkali metal between the right auricle and left ventricle may reflect the different function of these two chambers.

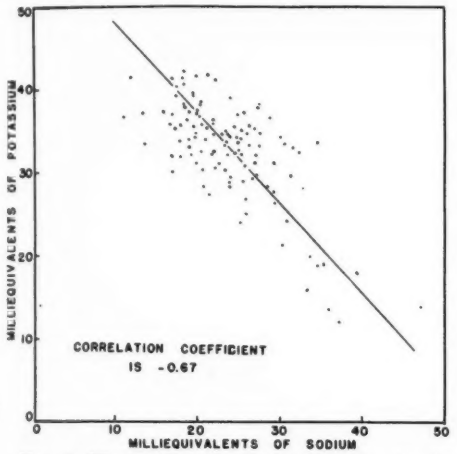

FIG. 2. The statistical relationship of potassium and sodium in dried heart tissue. The correlation coefficient is −0.67.

Heart enlargement is an important clinical sign of heart disease and edema of congestive heart failure, so it seemed important to determine whether the two necessarily bear any relationship. In figure 4, heart weights in grams on the abscissa are plotted against per cent water content on the ordinate. It is apparent that there is no relationship between heart weight and water content of heart muscle, for hearts weighing between 500 and 650 Gm. have the same average water content as hearts weighing between 200 and 300 Gm. This graph is representative of normal, diseased and digitalized diseased hearts. The relationship of heart weight and congestive heart failure to heart muscle chloride, sodium and potassium content is presented in table 3. The two hearts selected are representative of others in our series. The heart weighing 575 Gm. was that of a man dying suddenly from cerebral thrombosis. Prior to death he had had no pronounced heart symptoms and analysis showed the chloride, sodium and potassium content of his heart to be essentially normal despite its size.

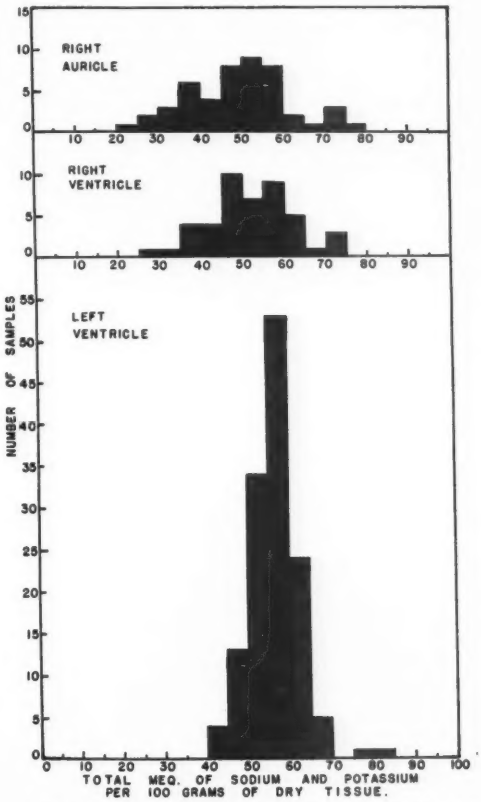
RIGHT AURICLE
RIGHT VENTRICLE
LEFT VENTRICLE
NUMBER OF SAMPLES
TOTAL MEQ. OF SODIUM AND POTASSIUM PER 100 GRAMS OF DRY TISSUE.

FIG. 3. The limits of variation of alkali metals in the right auricle, right ventricle and left ventricle.

The second heart weighing 250 Gm. was from a man dying with the clinical picture of congestive heart failure which followed intestinal surgery, prolonged use of gastric drainage by Levine tube and the administration of three liters of 5 per cent glucose in sterile water daily for 11 days. He received no saline solutions. He

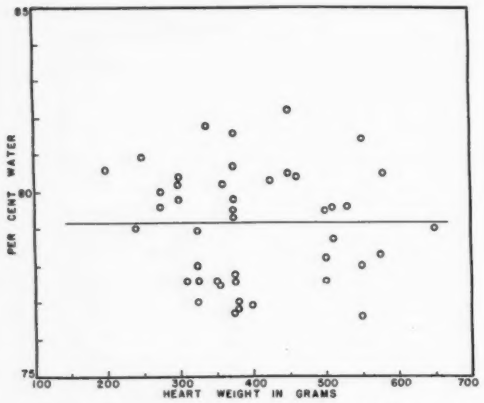

FIG. 4. The relationship of heart weight to water content. There is no correlation.

TABLE 3.—*Heart Weight and Electrolytes (per cent Wet Tissue)*

	H_2O	Na	K	Cl
Heart Weight 575 Gm. (compensated)				
Septum	78.5	0.100	0.318	0.13
Base Lt. Vent.	78.7	0.100	0.333	0.12
Apex Lt. Vent.	77.8	0.088	0.304	0.13
Heart Weight 250 Gm. (post-oper. glucose)				
Septum	79.9	0.056	0.287	0.06
Base Lt. Vent.	81.3	0.068	0.272	0.05
Apex Lt. Vent.	81.2			0.05
Averages	80.8	0.062	0.280	0.05

died after increasingly severe dyspnea, orthopnea, anasarca, weakness and ultimate collapse. The chemical changes in his heart are extreme, the left ventricular chlorides being 0.05 as compared with the normal of 0.12 with marked depletion of sodium to 0.062 per cent and potassium to 0.280 per cent, normal values being 0.0917 and 0.312 per cent respectively. He died with the clinical picture of congestive heart failure and with marked electrolyte change in the myocardium although with a heart of normal weight and no previous history of heart disease.

DISCUSSION

It has been stated[5] that the reduction in heart muscle potassium in congestive heart failure is the result of heart muscle edema. Our experience is to the contrary, as no real difference in average water content between normal and diseased hearts was found, although the latter show definite decrease in potassium content. Further, the potassium content of heart muscle of digitalized cardiac patients is higher than that of undigitalized cardiac patients with no or very slight change in the water content. Since heart muscle does not become edematous in congestive heart failure, changes in chloride or alkali metal content are not related to change in total heart muscle water.

There are distinct differences between the right auricle and left ventricle in chloride and electrolyte content and their behavior in congestive heart failure. Although the right auricle is more resistant than the left ventricle to quantitative change in individual metal content when congestive heart failure occurs, as shown by potassium-sodium ratios, nevertheless the right auricle has a wider range of total alkali metal content than does the left ventricle. These findings may reflect the varied importance of these electrolytes in the different functions of these two heart chambers.

In the isolated animal heart,[6] stimulation of the vagus nerve increased the potassium content of the perfusion fluid which was Locke's solution. The potassium loss was supposedly from heart muscle, and because the vagus nerve exerts greatest influence on the heart auricles, these chambers should contribute a greater proportion of their electrolyte content. We find that the auricle functions under a wide range of total electrolyte content but resists great change in individual electrolyte values. The right auricle is the location for the dominant stimulus formation, and these peculiarities of its electrolyte content may be necessary for maintaining the primary heart stimulus. At least it appears that sudden vagus stimulation

would not alter to any extent its potassium content. The left ventricle functions as the energy source for maintaining circulation of the blood. The energy producing or muscle contracting function of the left ventricle permits wide variation in individual electrolyte content with retention of the essential muscle irritability but exercises greater control over its content of total alkali metals. It seems possible that under certain conditions, strong vagus stimuli might quickly disturb auricular muscle potassium, alter impulse conductivity and produce an auricular arrhythmia such as occurs with severe, acute upper abdominal disease as duodenal ulcer and severe, acute gall bladder disease.

Various investigators[7-8] have noticed that potassium can abolish the extrasystoles that occur with overdigitalization. It has been assumed that the potassium content of heart muscle is reduced by such therapy but our studies show that digitalis restores rather than decreases the potassium content of heart muscle when in the state of congestive failure. On the basis of our findings it appears probable that, since digitalis does not fully replace the potassium-sodium balance, the giving of potassium may complete this restoration and thereby produce the results that have been observed.

A reciprocal relationship between sodium and potassium in heart muscle is suggested by this study. There is an increase in sodium and decrease in potassium when the heart muscle is in a state of congestive failure, although the total milliequivalents per 100 Gm. of dried heart tissue remain practically the same in normal and diseased hearts and the normal potassium-sodium ratios may be twice as large as in congestive heart failure. This suggests that the movement of one of these elements into or out of the muscle tissue is accompanied by the opposite movement of the other element.

The use of digitalis in congestive heart failure is reflected in nearer normal electrolyte values in all sections of digitalized diseased hearts as compared with undigitalized diseased hearts. This probably is produced by a direct chemical action of digitalis although central action through the vagus nerve under certain conditions may be a factor. We found that the lowered auricular muscle potassium in congestive heart failure is elevated toward normal by digitalis which indicates that the action of digitalis on the auricle is a direct chemical effect or that vagal stimulation does not decrease the auricular muscle potassium when the heart is in congestive failure.

As the total milliequivalents of alkali metals are the same in normal and diseased hearts, the giving of digitalis in congestive heart failure increases the potassium and decreases the sodium content of heart muscle, restoring the potassium-sodium ratio to nearer normal levels. However, the restoration by digitalis of the potassium-sodium ratios to within normal limits did not prevent death. Perhaps the reduced heart muscle potassium or the abnormal potassium-sodium ratio was of such long standing that irreversible myocardial cell damage was present. This could explain digitalis resistance or failure of clinical response and show the necessity for early and adequate digitalis therapy in cases of congestive heart failure.

Summary

A total of 50 human hearts, 16 from patients dying in congestive heart failure, were sectionally analyzed for water, chloride, sodium and potassium.

The total water content of normal, diseased and digitalized diseased hearts was the same. Therefore the water content of heart muscle is not the cause of changes in chloride or electrolyte content of heart muscle.

The milliequivalents per 100 Gm. of dried heart tissue of sodium increases and of potassium decreases in congestive heart failure but the sum of the two is the same in all hearts; this supports the existence of a reciprocal relationship between these cations in heart muscle tissue.

In congestive heart failure, digitalis restores the alkali metal values and ratios of heart muscle to near normal levels. The alkali metal changes produced by this drug in the right auricle and left ventricle are distinctly different. This may be related to the different function of these heart chambers.

Evidence is presented that digitalis exerts a

direct chemical action on the heart muscle and the possibility of irreversible myocardial damage with prolonged electrolyte unbalance suggests the importance of early and adequate digitalis therapy.

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The Measurement of Total "Sodium Space" and Total Body Sodium in Normal Individuals and in Patients with Cardiac Edema

By GEORGE F. WARNER, M.D., ERNEST L. DOBSON, PH.D., CAROLINE E. RODGERS, A.B., MURIEL E. JOHNSTON, M.A., AND NELLO PACE, PH.D.

Total sodium space and total body sodium contents were determined in four groups of individuals with the aid of radiosodium^{24}. There appears to be an increase in these values with age, but the presence of well compensated cardiovascular disease in the older age group does not significantly alter the magnitude of these measurements. When congestive failure with edema occurs, there is a marked increase in total sodium space and total body sodium. The increase in total sodium space shows a good correlation with the clinical degree of edema.

THE IMPORTANCE of sodium in the body economy is well known; however, reports of the measurement of the total "sodium space" in man have been infrequent. Kaltreider and co-workers[1] measured the volume of distribution following injection of radiosodium in a group of normal subjects. Recalculation of their data, allowing sufficient time for equilibrium to occur, shows an average value from three individuals for the total sodium space of 27.3 per cent of body weight. Fellers and associates[2] made five observations on normal adults and obtained a mean of 27.1 per cent of body weight, and Schwartz and associates[3] cite an average value of 26.6 per cent of body weight in three normal subjects. None of these authors, however, presents a study of the total sodium space in patients with cardiac edema.

Reports of the simultaneous measurement of total sodium space together with the total body sodium content in man have been even more infrequent. Shohl[4] gives an estimate of 63 Gm. for a 70 Kg. man (39 mEq. per kilogram) for total body sodium, and Moore[5] reported a value of 59 mEq. per kilogram in a single case using sodium^{24}. More recently, Forbes and Perley[6, 7] have used radiosodium to measure the total body sodium in a group of infants and young adults.

The present study has been primarily concerned with older age groups, and includes patients with cardiac edema as well as normal subjects. Four groups of individuals were chosen for comparison: group 1, consisting of young normal adults; group 2, old normal adults; group 3, old adults with cardiovascular disease but well compensated and edema-free; group 4, old adults with cardiovascular disease in congestive heart failure with edema. Total sodium space and total body sodium content of these four groups were determined.

METHODS

A single 10.0 ml. blood sample was obtained by venipuncture 24 hours after the injection of approximately 100 microcuries of sodium^{24} in sterile isotonic sodium chloride. The blood was allowed to clot and the serum removed. Duplicate 1.0 ml. samples of serum were dried on plates and the activity determined by means of a Geiger-Müller counter. The amount of sodium^{24} injected was determined by measuring the activity of an aliquot of the injected solution. All values were corrected for radioactive decay, background, and the resolving time

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of the counting equipment. In addition, the serum sodium[23] concentration of the samples was determined by flame photometry[8] by means of a Beckman flame photometer.

Calculations and Assumptions: The sodium[24] concentration of the serum samples relative to the total amount of sodium[24] injected represents the extent of dilution in the body of the injected dose. The volume of this dilution has been termed the total sodium space and can be expressed both in liters and as per cent of body weight. Thus, total

$$\text{sodium space} = \frac{\text{total sodium}^{24}\text{ activity injected}}{\text{serum sodium}^{24}\text{ concentration}}.$$

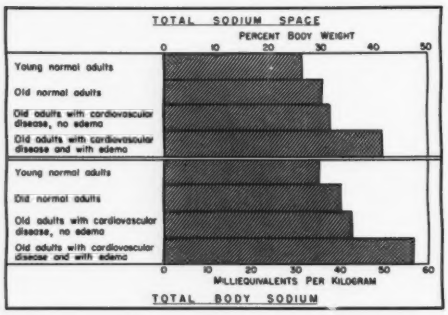

FIG. 1. Comparison of total sodium space and total body sodium in four groups of individuals.

TABLE 1.—*Sodium Spaces—Young Normal Adults*

Age	Height	Weight	Sodium space
years	*meters*	*kilograms*	*liters*
21	1.73	68.2	19.7
22	1.78	59.1	19.8
23	1.88	76.0	18.5
23	1.80	75.0	19.5
23	1.93	72.7	17.6
24	1.83	91.0	18.7
25	1.78	79.2	19.4
26	1.78	76.1	19.6
27	1.93	93.2	26.3
29	1.74	71.8	20.3

This calculation assumes a homogeneous concentration of sodium. Because sodium is not homogeneously distributed among the various tissues, the value obtained by calculation is virtual rather than actual. However, sodium space measurements are of considerable value when used comparatively.

The time of blood sampling after injection is important in determining the total sodium space. Burch and his colleagues[9] concluded from measurements of the sodium space made at 60 and 90 minutes that a total sodium space calculation made at these times cannot be accurate. Data to be published on measurements of 48-hour arterial plasma distribution curves indicate that a minimum period of 8 to 12 hours is required for complete equilibrium to be achieved. A 24-hour sampling time was found to be convenient and was chosen in this study, rather than a time of 8 to 12 hours, to allow more than the minimum time for equilibration to occur, particularly since many of the patients presented large amounts of edema.

The excretion of sodium[24] via urine, sweat, and feces over the 24-hour period was not measured directly. Unpublished data on sodium[24] blood distribution curves extended to 48 hours have shown the presence of a component which is believed to represent excretion. The slope of this component in young normal adults and in cardiac patients has indicated a loss of sodium[24] through excretion at the rate of 9 ± 3* per cent per day and 4 ± 2 per cent per day respectively. Ignoring this loss produces an artificial enlargement of the total sodium space amounting to 2.5 ± 0.8 per cent of the body weight in normal subjects, and to 1.5 ± 0.8 per cent of the body weight in cardiac patients with edema. The values reported here have been corrected arbitrarily for this excretory loss.

Assuming that at the end of 24 hours the specific activity of sodium is uniform throughout the body, the total body sodium may be obtained by multiplying the serum sodium[23] concentration by the total sodium space. The values for total body sodium determined in this manner have been expressed as milliequivalents per kilogram of body weight.

RESULTS

The results of total sodium space and total body sodium determinations in four groups of individuals are summarized in figure 1.

Group 1 consisted of 10 young normal adult males with an average age of 24.3 years (table 1). Total sodium spaces were determined in the manner described. The average value for the total sodium space in this group of young adults was 26.4 ± 1.1† per cent of the body weight. Direct serum sodium[23] levels were not determined in this group, but the normal value of 136 mEq. per liter given by Hald[10] was used to calculate the total body sodium contents. The average value for the total body sodium in this group was 35.5 ± 1.5 mEq. per kilogram; this value is somewhat lower than that given by Forbes and Perley.[6, 7]

* standard deviation

† standard error of the mean

Group 2 consisted of 13 old normal adult males averaging 57.9 years of age (table 2). The average value for the total sodium space was 30.3 ± 1.6 per cent of body weight. The total body sodium averaged 40.6 ± 1.5 mEq. per kilogram. The serum sodium[23] levels in this group averaged 136 mEq. per liter.

Group 3 consisted of 11 determinations on 10 old adult male patients with cardiovascular disease, usually hypertensive and/or arteriosclerotic, who were clinically well compensated and edema-free (table 3). The average age of this group was 54.0 years. The average value for the total sodium space was 32.2 ± 1.8 per cent of body weight, and the average total body sodium content was 42.8 ± 2.4 mEq. per kilogram. The serum sodium[23] levels in this group averaged 133 mEq. per liter.

TABLE 2.—*Sodium Spaces and Serum Sodium[23] Concentrations—Old Normal Adults*

Age	Height	Weight	Sodium space	Serum sodium[23]
years	*meters*	*kilograms*	*liters*	*mEq./liter*
42	1.79	54.1	16.9	138.3
44	1.65	71.8	26.1	137.8
48	1.74	69.5	22.7	130.8
50	1.80	70.5	23.0	139.5
51	1.63	69.5	18.2	139.5
51	1.60	52.7	18.5	140.3
52	1.91	70.5	25.1	127.2
57	1.65	53.2	16.5	136.2
64	1.88	95.5	22.5	138.7
69	1.67	64.3	20.9	131.2
70	1 71	56.8	19.0	132.8
71	1.57	54.5	25.0	144.3
83	1.70	52.3	19.3	137.2

Group 4 consisted of 20 determinations on 14 old adult males with cardiovascular disease, usually hypertensive and/or arteriosclerotic, who were decompensated (table 4). The majority of these patients were in critical degrees of congestive heart failure with marked elevations of venous pressure and prolongations of circulation time. Pulmonary congestion was often marked and dyspnea severe. Peripheral edema of mild to marked degree was present in all cases. Any patient with hypoproteinemia was excluded, and the use of mercurial or other diuretics was interdicted just prior to and during the determinations. The average age of this group was 61.3 years.

TABLE 3.—*Sodium Spaces and Serum Sodium[23] Concentrations—Old Adults with Cardiovascular Disease, Well Compensated and Edema-free*

Age	Height	Weight	Sodium space	Serum sodium[23]
years	*meters*	*kilograms*	*liters*	*mEq./liter*
40	1.83	57.7	16.1	130.1
45	1.64	61.4	19.8	125.7
50	1.78	66.6	23.0	124.8
50	1.85	84.1	24.2	139.2
51	1.78	86.1	35.6	133.3
57	1.71	63.6	27.6	134.8
58	1.79	64.1	15.6	135.8
61	1.76	69.3	23.1	146.0
73	1.72	97.3	31.6	135.9
75	1.73	76.8	27.2	127.8
75*	1.73	59.1	21.6	128.4

* Repeat determination.

TABLE 4.—*Sodium Spaces and Serum Sodium[23] Concentrations—Old Adults with Cardiovascular Disease, in Congestive Failure with Edema*

Age	Height	Weight	Sodium space	Serum sodium[23]	Clinical degree of edema
years	*meters*	*kilograms*	*liters*	*mEq./liter*	*plus*
40	1.79	65.5	32.2	137.0	3
49	1.62	68.4	31.8	138.7	3
49*	1.62	58.6	26.2	142.1	2
50	1.85	84.5	40.2	140.4	3
50*	1.85	83.6	33.7	139.0	2
56	1.71	87.0	42.3	142.4	4
56*	1.71	72.0	30.4	140.2	1
60	1.82	76.4	31.2	137.0	1
61	1.74	97.3	30.1	131.4	3
62	1.81	81.9	34.5	135.9	3
65	1.73	81.4	28.9	140.6	3
66	1.70	72.5	27.7	123.7	2
68	1.66	65.9	27.0	129.4	2
69	1.82	60.0	28.3	141.8	3
70	1.73	77.5	41.2	126.6	4
70*	1.73	68.0	34.8	136.6	3
70*	1.73	59.1	23.0	128.2	1
71	1.75	107.3	36.0	130.0	3
72	1.72	54.5	29.3	138.1	3
72*	1.72	50.2	22.1	126.2	2

* Repeat determinations.

The average value for the total sodium space was 41.7 ± 1.5 per cent of body weight. The average value for the total body sodium was

56.7 ± 1.9 mEq. per kilogram. The average serum sodium[23] concentration was 135 mEq. per liter.

Discussion

It can be seen from figure 1 that there is a difference in total sodium space and total body sodium content between the young and the old normal adults. The presence of well compensated cardiovascular disease, however, does not appreciably increase the values in the older age group. When congestive failure with peripheral edema is present, there is seen a marked increase in the total sodium space and the total body sodium content.

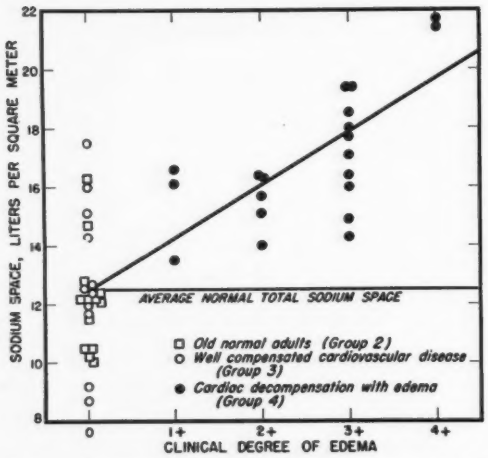

Fig. 2. Comparison of individual measurements of sodium space with clinical estimate of edema.

Prior to measurement, a clinical estimate of edema was made on an arbitrary scale from plus 1 to plus 4. The best correlation between the total sodium space and the amount of estimated edema has been obtained by expressing the sodium space as liters per square meter of body surface. Ideally, comparisons of body composition between individuals should be made on a fat-free body weight basis[11]; however, lacking this data an approximation may be made by expression of the results on the basis of body surface area. The total sodium spaces expressed in this manner are shown in relation to the clinical degree of edema in figure 2.

In figure 2, the horizontal line represents the average normal total sodium space in liters per square meter. The diagonal line shows the increase in total sodium space with increasing amounts of edema. The correlation coefficient has been calculated to be 0.77. The difference between these two lines at any point represents the excess total sodium space, and varies in an average individual (1.73 square meters) from approximately 3 liters of sodium space in minimally detectable edema to about 13 liters of sodium space in markedly edematous patients.

It is well known that the volume of distribution of sodium is larger than the volume of distribution of certain other substances (thiocyanate, sucrose, inulin, mannitol) which are thought to measure the extracellular fluid compartment. The reason for this discrepancy is that sodium is not limited to the extracellular fluid compartment but is also found in tissue cells and in bone. When congestive failure with edema occurs, there is an expansion of the volume of distribution of sodium (total sodium space). The increase in total sodium space correlates closely with the clinical degree of edema. This suggests that the expansion of total sodium space may be primarily an increase in the extracellular volume and that the excess sodium space in edematous cardiac patients represents the actual increase of body fluid (extravascular extracellular) constituting the edema. However, the possibility of an increase in the other body sodium compartments, for example, intracellular space and bone, is not ruled out. Quantitative conclusions on the distribution of the sodium within the total sodium space cannot be made on the basis of presently available data.

Summary

Total sodium space and total body sodium contents were determined in four groups of individuals with the aid of radiosodium[24]. There appears to be an increase in these values with age, but the presence of well compensated cardiovascular disease in the older age group does not significantly alter the magnitude of these measurements. When congestive failure with edema occurs, there is a marked increase

n total sodium space and total body sodium. The increase in total sodium space shows a good correlation with the clinical degree of edema.

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Thrombocytic Acroangiothrombosis

Febrile Anemia, Thrombocytopenia, and Thromboses of Damaged Capillaries and Arterioles

By HALL S. TACKET, M.D., AND RUSSELL S. JONES, M.D.

Two additional cases of a syndrome characterized by arthralgia, fever, anemia, thrombocytopenia, hemorrhagic manifestations, and thromboses of arterioles and capillaries are presented Pathologic description is given in some detail. Resemblances to certain other processes, including the rickettsial diseases, "vascular collagen" diseases and other conditions are pointed out. Deficiencies in knowledge of the entity are emphasized and a plea is made for continued efforts to define precisely the natural history of the syndrome.

IN RECENT years a new and distinct syndrome comprising fever, arthralgia, thrombocytopenia, anemia, focal neurologic signs and hemorrhagic tendencies has been defined. Thus far the disease has been diagnosed conclusively only at autopsy. The specific pathologic changes consist of widespread thromboses in capillaries, arterioles, and occasionally in venules. These thrombi, composed of hyaline material, platelets, and proliferating endothelial cells, are associated with alterations in the vessel walls. The syndrome is a nosologic entity and has been given various designations that vary in emphasis placed upon specific clinical or histologic features: "Thrombotic thrombocytopenic purpura," "thrombocytic acroangiothrombosis," "generalized (or disseminated) capillary and arteriolar platelet thrombosis," "acute febrile anemia and thrombocytopenic purpura with vasothromboses," and "diffuse platelet thromboses with thrombocytopenia and hemolytic anemia."[1–7] The syndrome is being recognized with increasing frequency, and approximately 30 cases have now been reported in the literature since the original description by Moschcowitz[1] in 1925. There have been several reviews of the reported cases, the first in 1936[2] and two others in 1947.[3, 4]

Since the diagnosis can be established at the present time only by the recognition of the characteristic vascular changes at autopsy, it is obvious that the natural history of the disease is incomplete. There may be mild and transient or relapsing and chronic forms that are nonfatal. The failure of clinical recognition even of the reported severe and fatal cases is reflected in the lack of careful search for etiologic agents. Complete serologic, bacterial and animal inoculation studies have not yet been made. While the etiology is unknown and the natural history poorly defined, the syndrome is of considerable interest in its possible relationship to the rickettsial diseases, to the "vascular-collagen" group such as lupus erythematosus, polyarteritis nodosa and rheumatic fever, and to allergic phenomena in general. The difficult clinical differentiation of thrombocytic acroangiothrombosis from such diseases, and particularly from thrombocytopenic purpura, justifies dissemination of information regarding each case as it becomes recognized. Thus, the diagnosis of future cases may be more timely established and investigation of etiology and effective therapy may be stimulated.

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CASE REPORTS

Case 1. A 45 year old Negro male with a painful, inflamed, left eye was seen on Dec. 8, 1948. Weight loss of 15 pounds had occurred during the preceding three months, and weakness and pain in the hips and thighs, aggravated by activity, had been present for two months. A diagnosis of iridocyclitis was made. The patient received six intramuscular injections of 10 ml. of milk each during the ensuing three weeks. Two weeks later the patient began to suffer from severe, constant, left supraorbital headache. On

Jan. 3, 1949 he awakened with diplopia and inability to open the left eye. Physical examination disclosed ptosis of the left eyelid, slight left exotropia, and inability to move the eye upward, medially, or downward. Red blood cells numbered 4.02 million per cu. mm., white blood cells 7,850 and hemoglobin 11.5 Gm. per 100 ml. Platelets numbered 2 to 3 per oil immersion field. There were 95 per cent polymorphonuclear leukocytes, 4 per cent lymphocytes, and 1 per cent large mononuclear cells. The urine contained 2 plus albumin and innumerable leukocytes and occasional erythrocytes. Serum bilirubin was 0.3 mg. direct, 2.0 mg. total. Following cystoscopy, at which a few, small, scattered petechiae were noted in the mucosa of the bladder, massive hematuria persisted until the patient's death. Hemorrhages developed in the eye grounds and skin of the arms. On January 19, the platelets numbered 29,000 per cu. mm. (Rees-Ecker). The reticulocyte count was 12.5 per cent. The bleeding time (Ivy) was longer than 29½ minutes. The clotting time was 5 minutes. No increased capillary fragility was demonstrated. Prothrombin time was 100 per cent. The bone marrow showed many mitoses in the erythroid series and many megakaryocytes. Cellular distribution was approximately normal. Fever ranging from 99 F. to 104 F. persisted throughout hospitalization. Splenectomy was done as a last resort; the patient expired 40 minutes after completion of the operation.

Pathologic Findings

The only important gross changes were hemorrhages in the brain, gastrointestinal tract and urinary tract. The vascular changes were most prominent in the adrenal glands, myocardium, spleen, brain, kidneys and urinary bladder.

The brain presented several 3 mm. areas of hemorrhage in the brain substance. Microscopically, granular and hyaline masses occluded the lumens of small veins, arterioles, and capillaries, most frequently in the cerebral cortex. Proliferation of the endothelium not only accompanied these thrombi, but often occurred where no thrombi were present.

Microscopic changes in the small vessels of the myocardium were marked. In the capillaries endothelial proliferation was prominent, while in arterioles and venules the smooth muscle cells of the media were also of increased prominence. Between the enlarged and proliferated medial and endothelial cells, there were zones of vacuolization and granular homogeneous material which appeared to project into the lumen, raising the endothelium above it. Less frequent than these changes were granular, eosinophilic thrombi in the vessel lumens. These thrombi were usually attached to one portion of the wall, leaving a crescentic portion of the lumen unoccluded. Some of these intraluminal masses contained huge and bizarre nuclei, either the aggregation of several nuclei or a single nucleus. Several small vascular lesions were older than others, for partial organization by fibroblastic cells and collagen fibers had already occurred. Occasionally, the adventitial connective tissue contained a few mononuclear leukocytes and some macrophages laden with ochre-colored pigment.

Many of the pulmonary capillaries and several small pulmonary arteries contained finely granular thrombi with the previously described alterations in their walls. The same vascular changes were present in the spleen and liver. The adrenal glands were the sites of the most extensive vascular changes. These changes, similar to those already described in the myocardium, extended only a short distance into the cortex, leaving the sinusoids of the inner zones intact. The arterioles to the renal glomeruli, those among the convoluted tubules of the cortex and about the pericalyceal tissue occasionally showed areas of vascular change similar to that described in other organs. The characteristic mural and luminal changes were seen in the mucosa and muscularis of the urinary bladder, associated with hemorrhage and moderate numbers of mononuclear leucocytes in the adjacent connective tissue.

The bone marrow presented a few vessels with the characteristic vascular changes. The megakaryocytes were present in the usual number and possessed the usual morphologic features. Other cells of the bone marrow showed no significant changes.

Case 2. R. L. L., a 54 year old white man, had had cavitary pulmonary tuberculosis during the four years prior to his terminal episode. In May, 1951, he began to complain of malaise, weakness, and mild headache. Three days later he was found lying in bed with motor aphasia. He became semicomatose and had a slight convulsion followed by vomiting. Fever ranged between 100 and 104 F. (rectal). The urine contained 2 to 4 plus albumin and few to many casts and erythrocytes. Blood nonprotein nitrogen ranged from 53 to 65 mg. and creatinine from 3.4 to 3.8 mg. per 100 ml. The cerebrospinal fluid was normal. The red blood cell count ranged between 2.86 million and 1.93 million per cu. mm., the hemoglobin between 8.5 and "less than 7.5" Gm. per 100 ml., the white blood cell count between 8,400 and 6,900 per cu. mm. with polymorphonuclear leukocytes between 66 and 57 per cent, lymphocytes from 22 to 27 per cent, monocytes from 3 to 13 per cent, and eosinophils from 3 to 9 per cent. There was no estimation of the number of platelets. Bleeding time was 6 minutes, 35 seconds, coagulation time 7 minutes, 20 seconds. No acid-fast bacilli were found on direct smear of the sputum. Death occurred within a week following progressively deepening coma.

Pathologic Findings

The significant gross changes consisted of splenomegaly, cardiomegaly, petechial hemorrhages over the extremities, epicardium, and gastrointestinal tract, and pulmonary tuberculosis. The vascular

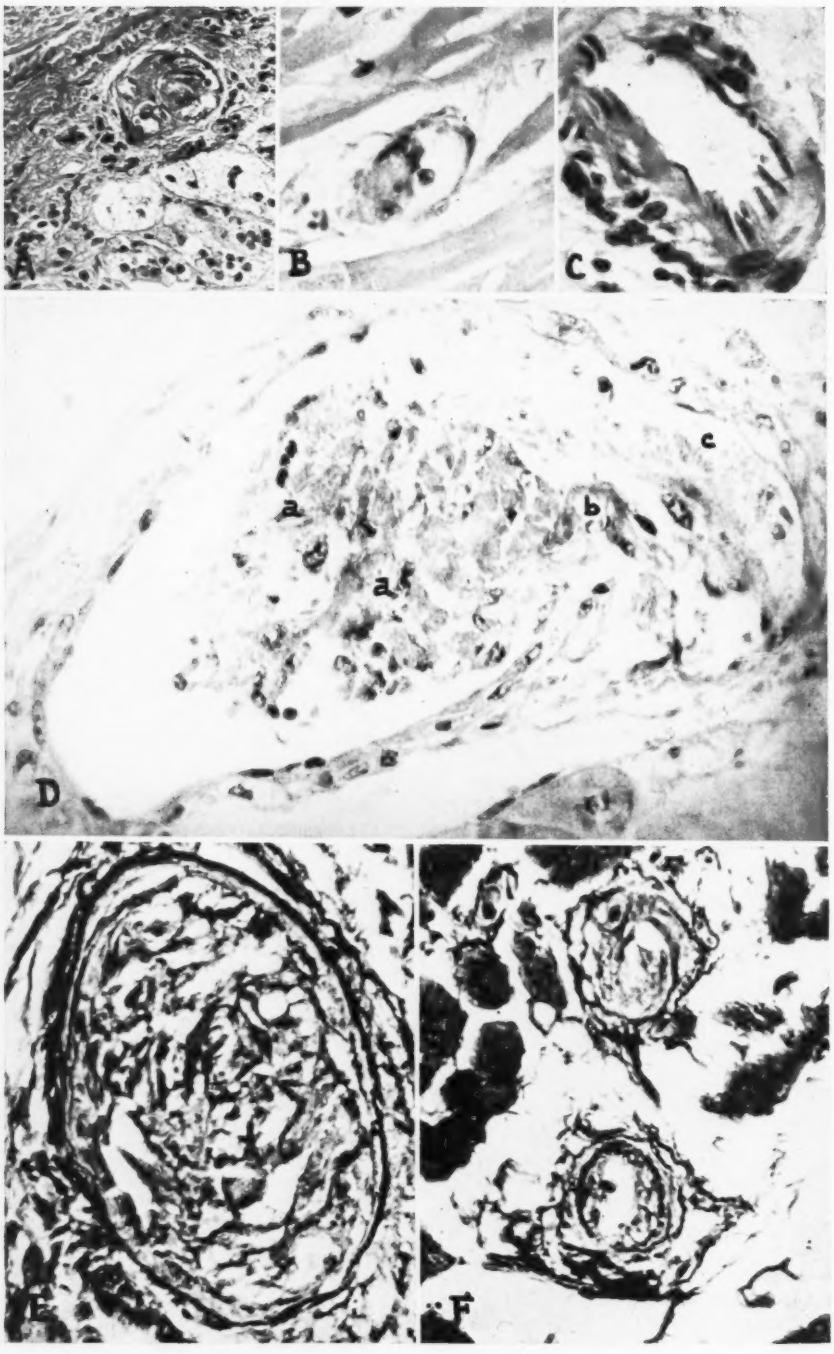

FIG. 1. Legend on facing page.

wall changes and "hyaline" thromboses were most marked in the myocardium, kidneys, adrenal glands, posterior lobe of the pituitary, and pancreas. The brain showed the same vascular wall changes, and granular and hyaline thrombi in the arterioles and capillaries as were noted in the first case. There was considerable involvement of the small vessels of the posterior lobe of the pituitary. The heart was soft and pale with scattered petechial hemorrhages throughout its substance and over its surface. Microsections showed disruption of the vessel walls by vacuolization and granular material with occlusion of the lumina partially or completely by "hyaline" masses containing variable numbers of endothelial or fibroblastic cells. A few of these thrombi appeared older than others, being replaced by older fibroblasts and collagen. About such vessels a moderate number of mononuclear leukocytes with basophilic cytoplasm was present. A number of capillaries showed marked proliferation, of endothelium without luminal masses.

Scattered caseonodular lesions were present throughout both upper lobes of the lung and groups of tubercles were present in the apical portions of both lower lobes. No vascular changes consistent with acroangiothrombosis were found in the pulmonary tissue either about or away from the sites of the tuberculous lesions. Some arterioles of the spleen, pancreas and retroperitoneal lymph nodes showed the characteristic mural and luminal changes. Changes in the adrenal vessels were less marked than in the previous case. Many small arteries, arterioles, and capillaries of the kidneys showed the mural and luminal changes. A few hyaline thrombi were seen in the capillary tufts. The parietal epithelial cells of Bowman's capsule were of increased prominence.

Discussion

Clinical and Laboratory Findings. The characteristic listlessness and malaise of this syndrome were not as outstanding in the first patient as in the second. Central nervous manifestations in our patients were less prominent than in many of the previously reported cases. The only neurologic lesion demonstrated involved the left third cranial nerve. The frontal headache in the first case could have been due to either iridocyclitis or intracranial vascular disease. Hepatosplenomegaly was not observed in the first patient and was slight in the second. The febrile course is characteristic of thrombocytic acroangiothrombosis. Purpura was outstanding in both patients. The persistence and unusual severity of the hematuria in the first case finally led to splenectomy as the therapeutic procedure of last resort.

The laboratory findings, most complete in case 1, were typical: the severe anemia, the prolonged bleeding time and normal clotting time, the thrombocytopenia, the hyperplastic bone marrow, and mild elevation of serum bilirubin. The negative tourniquet test, however, in our first case is contrary to the observation of this test in the majority of other reported cases.

Clinically, thrombocytic acroangiothrombosis is most readily mistaken for idiopathic thrombocytopenic purpura. The following features may be more outstanding in thrombocytic acroangiothrombosis than in idiopathic thrombocytopenic purpura[4]: (1) splenomegaly, (2) jaundice, (3) fever, (4) prodromal symptoms of weakness, malaise, and joint pains, (5) focal

Fig. 1. Examples of mural and luminal changes in thrombocytopenic acroangiothrombosis.

A. Arteriole in the adrenal capsule shows marked changes in its wall and obliteration of most of its lumen. Masson stain × 225

B. Myocardial capillary with small thrombus partially covered by endothelial cells. Hematoxylin and eosin × 535

C. Small artery in myocardium with focal vacuolization of media and some increase in the subintimal tissue. Hematoxylin and eosin × 535

D. Branching epicardial vessel with thrombus containing endothelial cells, collagen and reticulin fibers interspersed among amorphous material (a) "fibrinoid" changes, (b) at point of branching, and loosely aggregated particles, apparently platelets (c). Masson ×460

E. Small artery with interrupted elastica interna and a lumen distended and occluded by endothelial and fibroblastic cells, collagen, reticulin and amorphous material. This represents an older, and more marked process than that in *D*. The thrombotic mass is undergoing healing. "Fibrinoid" changes—i.e., the reddish staining with fragmentation of collagen with Masson stain—was present in the adjoining tissue. Combined connective tissue stain (elastic, reticulin and collagen) × 535

F. The elastica interna of the lower arteriole is almost intact while that of the upper arteriole is no longer visible. There are some medial changes and moderate subintimal increase in both arterioles. This subintimal and luminal material is Schiff-positive and the reticulin fibers are of increased distinctness. Orcein-silver stain for elastin and reticulin × 535

neurologic signs rather than massive cerebral hemorrhages, (6) transient leukemoid blood picture, (7) anemia disproportionate to observed blood loss, and (8) frequent association with sensitivity phenomena. While these findings lead one to suspect thrombocytic acroangiothrombosis in a patient with purpura and thrombocytopenia, the syndrome cannot be positively diagnosed at the present time without the histologic demonstration of widespread thrombosis of the arterioles and capillaries in association with changes in the walls of these vessels.

Pathologic Changes. In thrombocytic acroangiothrombosis, there are changes in vessel walls as well as thromboses within the vessels. Some writers have thought that the thromboses were the initial lesions, but Altschule[8] and later Trobough[9] suggested the primary defect to be in the vessel wall at the arteriolocapillary junction. Gore's[10] reconstruction of the development of the thrombotic lesions confirms these observations and concurs with the findings in our two cases. Apparently there is an initial accumulation of vacuoles of unidentified content and granular, hyaline material in the arteriolar or capillary wall. The granular material, which stains red with the leukofuchsin, accumulates predominantly within the intima and above the elastica interna. The latter becomes fragmented and may disappear. With the continued accumulation of material, it may rupture externally, causing hemorrhage into the surrounding tissues. It also extrudes intraluminally where the material is rapidly covered by aggregates of platelets and then by endothelial and fibroblastic cells. The thrombus may propagate along the length of the vessel, which is usually quite distorted and which may present focal aneurysmal dilations.[11] Perivascular leukocytic response is mild. There is mild "fibrinoid" alteration in portions of the vessel wall and in the perivascular connective tissue.

The older elongated fibroblasts and the collagen fibrils in some of the thrombotic lesions suggest that the lesions are of different ages, but there is no conclusive evidence that they occur in "crops." The granular mural material and intraluminal mass is red in color with periodic leukofuchsin (Schiff) stain, orange-red with phosphotungstic acid, red with Giemsa and with hematoxylin and eosin, and red to green with Masson stain. Fat stains indicate that it has no lipid content. It is obvious that the exact nature of the material cannot be determined by these staining procedures. Many vessels showed changes in the wall without accompanying thrombi and many of the "thrombi" in our two cases actually consisted of this mural substance. Unmistakable groups of platelets and even a few leukocytes and erythrocytes were sometimes incorporated in and about these masses, however. Healing apparently occurs by the deposition of collagen and reticulin about fibroblastic and endothelial cells in the thrombus.

Pathogenesis. It is evident that definition of predisposing and inciting causes of thrombocytic acroangiothrombosis is entirely speculative. Primarily because of the lack of clinical recognition of this syndrome, complete studies in an effort to demonstrate an infectious etiologic agent have not yet been made. Exploration of relationships and similarities to other diseases gives some clues, of perhaps dubious value, to the underlying cause of the syndrome.

In common with many diseases, especially those of the vascular system such as polyarteritis nodosa, temporal arteritis, thromboangiitis obliterans, idiopathic migratory thrombophlebitis and even arteriolosclerosis, this syndrome represents an entity established by a combination of clinical and pathologic findings. Only severe and fatal cases have been recognized and recorded in the literature, and many less severe cases may remain unrecognized. Its relation to other syndromes of unknown etiology and uncertain pathogenesis remains obscure. For example, an atypical case of disseminated lupus erythematosus may present many of the features of thrombocytic acroangiothrombosis such as splenomegaly, anemia, thrombocytopenia, purpura, hematuria, arthralgia, and even arteriolar and capillary thromboses.

Purpura is generally classified by the presence or absence of an inciting agent and of thrombocytopenia. Apparently the arteriolocapillary junction is the site of vascular rupture both in nonthrombocytopenic purpura and

in the thrombocytopenic form. This site of vascular rupture was shown by Humble[12] to be common to a wide variety of purpuric conditions. The arteriolocapillary junction is, also, the predominant site of vascular damage in acroangiothrombosis,[9] suggesting a relationship between this disease and other purpuras. However, no mural damage or thrombi have been observed in cases of either secondary or primary thrombocytopenic purpura by Nickerson and Sunderland[13] or by us in a review of autopsies of patients with thrombocytopenic purpura.

The cause for the reduction in platelets in idiopathic thrombocytopenic purpura is not conclusively established. The relative rates of intravascular accumulation and lysis of platelets are proposed by Gore[10] as factors determining the presence or absence of the platelet thrombi in acroangiothrombosis. It is conceivable that the thrombocytopenia in both syndromes may arise from the same mechanism, and the absence of vascular thrombi in thrombocytopenic purpura may be due to preponderance of factors favoring lysis of platelets. The thrombocytopenia of thrombocytic acroangiothrombosis has been attributed to exhaustion of circulating platelets by the formation of platelet thrombi. Recent indications that the thrombi are composed largely of material other than platelets may require revision of this concept.

Hyaline thrombi occur in the arterioles and capillaries in many different diseases, for example, arteriolosclerosus with uremia, septicemia, disseminated lupus erythematosus, and sulfonamide reactions. The wide dissemination of thrombi in arterioles and capillaries whose walls are altered assists in the morphologic distinction of thrombocytic acroangiothrombosis from these conditions. Among other diseases resembling thrombocytic acroangiothrombosis are certain rickettsial diseases. Fever, headache, mental symptoms, prostration, myocarditis, pulmonary vasculitis, petechial hemorrhages in viscera, and a purpuric rash with arteriolar necrosis and thromboses are features in common. Morphologic distinctions in epidemic typhus and Rocky Mountain spotted fever are based on the prominent perivascular leucocytic infiltration and endothelial cell damage without the occurrence of thrombi. Although in cases of scrub typhus platelet thrombi may be found in the eschar, the rash, and infrequently in the septal capillaries of the lung or the glomerular tuft capillaries of the kidney, the predominant involvement of the venules and veins, the occurrence of "typhus nodules" in the brain, and certain "allergic" responses such as fibrinoid necrosis of collagen, necrosis of lymph nodes and spleen, and a characteristic cellular infiltrate serve to differentiate the two conditions.[3, 14] Rickettsia may be demonstrated in the swollen endothelial cells of the altered vessels.

Toxoplasmosis in the adult may also be similar both clinically and pathologically to thrombocytic acroangiothrombosis. The presence of a red maculopapular skin eruption and the absence of focal neurologic signs, thrombocytopenia, and profound anemia assist in the clinical differentiation. Although uveitis may occur, the ocular lesion is usually chorioretinitis.[15] Toxoplasma may be identified in the cutaneous papules, the cerebrospinal fluid, the bronchioles, and the myocardium. Hyaline thrombi are not prominent.[16]

Although thrombocytic acroangiothrombosis resembles in several respects diseases of rickettsial or other infectious origins, there are, also, indications of a possible allergic etiology. Little is gained from grouping this syndrome as an allergic disease, for "allergy" or "hypersensitivity" itself is a most nebulous and poorly understood body response which has gained a false distinction through long uncritical usage. The body responds to each disease due to a known etiologic agent, including the rickettsial diseases, with some component of "allergy" and "immunity." In Ehrich's case the disease seemed to follow the administration of an iodine compound. Some reported patients have had a history of sensitivity to sulfonamide drugs,[6] and others have had urticaria.[3] The importance of a reaction to nonspecific protein therapy, consisting of intramuscular injections of milk, in the genesis of our first case is an intriguing consideration. Such therapy could have aggravated milder lesions characterized by iridocyclitis, malaise, and arthralgia. The possibility exists that certain therapeutic measures and other

circumstances may precipitate or aggravate a nonspecific body response, resulting in the complete development of this syndrome. Thrombocytic acroangiothrombosis cannot yet be relegated to the allergic group of vascular and connective tissue responses, at least until there has been a careful search for etiologic agents.

Summary

Two additional cases of a syndrome characterized by fever, anemia, hemorrhagic manifestations, central nervous symptoms, and the occurrence histologically of thrombotic occlusions of capillaries are presented. The two cases, in general, were analogous to the previously reported cases with quantitative rather than qualitative variation in symptomatology from them. The synthesis of clinical and pathologic data in these cases comprises a discrete nosologic entity. There are, however, resemblances to other processes including thrombocytopenic purpura, rickettsial diseases, certain allergic phenomena, and the large group of vaguely defined "vascular collagen" diseases such as disseminated lupus erythematosus and polyarteritis nodosa. Various clinical and pathologic features permit differentiation from such diseases. The cause of the condition remains obscure, although similarities with other diseases of known etiology, particularly the rickettsial group, may give some hint of the nature of the inciting agent. Sufficient investigation with respect to a possible infectious etiology has not yet been done to permit exclusion of such causation. Until all etiologic possibilities have been evaluated, categorization of the entity as a manifestation of allergy, as has been previously suggested, is not justified.

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CLINICAL PROGRESS

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The Anesthetic Management of Patients with Heart Disease

By ROBERT D. DRIPPS, M.D., AND LEROY D. VANDAM, M.D.

IN THIS era of direct investigation in man a number of measurements have been made of the hemodynamics of congestive heart failure, mitral stenosis, various types of congenital heart disease, hypertension and coronary artery disease. Cerebral, coronary, renal and hepatic blood flow have been measured, as have cardiac output and venous right auricular and pulmonary vascular pressures. Similar studies of the circulatory actions of anesthetic agents have been begun. Ideally a discussion of the anesthetic management of patients with heart disease should relate these two groups of data. Thus, for example, if a fundamental property of a particular drug were the production of pulmonary artery hypertension, this substance might be contraindicated when the pressure was elevated by disease. Unfortunately, only fragmentary analyses have been completed and it is not yet possible to be certain on the basis of physiologic data that one form of anesthesia is the best in a given situation.

This paper represents primarily the personal opinions of the authors. It is not to be regarded as a review of the literature. The circulatory effects of the more commonly used anesthetic agents and technics will be briefly outlined. Comments on our procedure for evaluation of patients will be presented. The management of certain groups of patients will be discussed in the light of our clinical experience. A final section will deal with the cause, prevention, therapy and significance of cardiac arrhythmias noted during anesthesia and operation.

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I. Anesthetic Agents and Technics

1. Cyclopropane. This substance is an extremely useful anesthetic agent because of its potency, smoothness and rapidity of induction and emergence, and rapid controllability. Certain alterations in the circulation may follow its use. These must be understood and evaluated before cyclopropane can be assigned its proper place in anesthesia. The drug may cause any or all of the following changes:

a. A rise in arterial pressure during anesthesia.

b. A rise in central venous and right auricular pressure.

c. A decreased arteriovenous oxygen difference.

d. A decline in blood pressure below preoperative levels at the conclusion of anesthesia. When marked this response has been termed "cyclopropane shock."

e. Abnormalities of cardiac rate and rhythm.

The factors responsible for these alterations are still not clearly defined. Certain speculations can be made, however. The first three items suggest that the rate of blood flow is more rapid under cyclopropane and that blood is shifted more promptly from the arterial to the venous side of the circulation. Arteriovenous shunts may be opened. Redistribution of blood may occur so that certain areas no longer receive as much of a supply of blood as they normally do. The rise in central venous pressure may be responsible for the rise in

cardiac output which has been reported by some workers. This in turn may be responsible for the rise in arterial blood pressure. Increase in central venous pressure has also been attributed to partial incompetence of the heart, a possibility which deserves further investigation. The clinical significance of these alterations of the circulation to the patient with cardiovascular disease is not at once apparent unless under exceptional circumstances the increase in blood pressure or cardiac output were such as to overstrain a damaged heart. Clinically, this must be a most unusual circumstance.

Postcyclopropane hypotension may pose a problem to the individual with low cardiac reserve, particularly to the patient with coronary insufficiency. At least one factor responsible for this postanesthetic decline in blood pressure is the respiratory acidosis which may accompany underventilation with any agent, be it cyclopropane, pentothal, curare or any other respiratory depressant. This syndrome is therefore largely preventable. It involves maintenance of adequate respiratory exchange during anesthesia. Clinicians have learned to minimize this disorder by maintaining a more normal respiratory exchange during anesthesia.

The abnormalities of cardiac rate and rhythm are of two types. The first are slow rhythms, caused by a downward displacement of the pacemaker and probably related to parasympathetic stimulation and increased vagal tone. These slow rhythms are of little clinical importance. The second are more rapid rhythms caused by increased irritability of the myocardium. There may be ventricular extrasystoles, ventricular tachycardia or, very rarely, ventricular fibrillation.

A great deal of experimental work has been reported on the underlying mechanism of this increased irritability. The ability of cyclopropane to produce increased myocardial irritability and abnormalities of rate and rhythm is not peculiar to this agent alone but is characteristic of a large group of hydrocarbons such as butane, gasoline, methane, carbon tetrachloride, DDT, xylocaine and many others. The action of any one of these substances alone, however, is rarely sufficient to produce an evident arrhythmia. Apparently a trigger mechanism is necessary, the most easily demonstrable of which is that initiated by epinephrine.

Ventricular tachycardia and fibrillation can be produced by the injection of epinephrine into animals or man receiving cyclopropane anesthesia. If one avoids injecting epinephrine, the only other source of epinephrine would be endogenous. Presumably epinephrine could be mobilized by anoxia, pain, increased carbon dioxide and so forth. In this way a sufficient amount might be liberated to precipitate an arrhythmia in the presence of cyclopropane.

We grant that ventricular tachycardia may not be uncommon during cyclopropane anesthesia if this drug is used alone. An incidence of 10 per cent has been suggested by some. If, as is done by most clinicians, ethyl ether is added in small amounts, the incidence of ventricular tachycardia is significantly reduced. Furthermore, clinical experience indicates that ventricular tachycardia is relatively rarely followed by ventricular fibrillation on the operating table. Many instances of ventricular tachycardia are reported in the literature. Authentic reports of ventricular fibrillation occurring during cyclopropane anesthesia are extremely rare. Sudden circulatory collapse may occur during cyclopropane as with any other powerful depressant. Such a catastrophe cannot be assumed to be due to ventricular fibrillation unless an electrocardiogram were being taken at the time or unless the heart were visualized directly and seen to be in fibrillation. The most common cause for such a calamity is overdose of the anesthetic agent.

We have anesthetized many patients with serious cardiac disease with cyclopropane and small amounts of ether. It is our belief that the opponents of this agent have somewhat exaggerated the possibilities of harm following its use and have overlooked the advantages of smooth induction, relatively prompt recovery and controllability. Many of the circulatory alterations which have been discussed can be prevented, minimized or treated successfully. The mortality rate following cyclopropane is difficult to assess but in our clinic it does not appear to be excessive. The comparative incidence of postoperative circulatory complication is even more difficult to define in terms of

different anesthetic agents. Again our experience indicates that serious sequelae have been no more frequent with cyclopropane.

Since so many agents and technics are available to the modern anesthesiologist, it is probably wise to avoid use of this agent in the presence of thyrotoxicosis or other instances in which myocardial irritability is known to be increased.

2. Ethyl Ether. There are many characteristics which suggest the use of this anesthetic agent for patients with cardiovascular disease. There is a wide margin between the concentration of the drug required to produce respiratory failure and that required to produce circulatory failure. During anesthesia, fluctuations of blood pressure are much less common than with other anesthetics, other things being equal.

A great many misconceptions about ether have arisen because of the very safety of the agent which permitted individuals of varying skill to administer the drug without obvious harm to the patient. The unskilled administration of ether is followed by increased secretions in the respiratory tract, swallowing of ether-laden mucus, by anoxia and carbon dioxide retention. The latter are particularly likely to occur if excessive amounts of gauze are used on the mask or if the gauze becomes soaked with water vapor during an open drop anesthesia. We believe that one of the disadvantages of ether is the prolonged period of induction occasionally required. A hurried induction may be accompanied by cough, excessive secretions, respiratory obstruction and excitement. These sequelae, however, need not invariably occur and are less commonly seen when the drug is administered by capable personnel.

The work of Zweifach, Chambers and associates suggests that there may be a disintegration of the circulation during anesthesia with ether when an animal is subjected to hemorrhage. Compensation appears to be less adequate than with cyclopropane and a vasodepressor substance seems to be liberated. If this work is confirmed for man, there may be significant clinical implications. At the moment, however, ether stands as an exceptionally valuable anesthetic agent.

3. Nitrous Oxide. This relatively weak anesthetic agent cannot be administered by itself for major operations without the deliberate production of some degree of anoxia unless the patient is in shock or debilitated. The drug causes little postoperative disturbance of function and is therefore of great value when its potency is increased by the concomitant use of some other central nervous system depressant such as an opiate or barbiturate. If muscular relaxation is not required for an operation, such a combination may be extremely useful in that recovery from anesthesia is usually prompt and uneventful.

4. Pentothal. The outstanding advantage of this substance for the patient with cardiac disability is the smooth induction afforded. Excitement is absent and there is relatively little strain. If larger doses are used, however, and if the anesthetist attempts to obtain a deeper plane of anesthesia, tachycardia and hypotension are not infrequent.

It should be recalled that the barbituric acid derivatives are not analgesics. They do not block sensory pathways as readily as do most narcotics, so afferent impulses from the operative site can readily reach the cerebral cortex. In response to surgical manipulations, reflex spasm of the vocal cords with respiratory obstructions and anoxia, reflex spasm of abdominal muscles, or actual movement of the patient may occur.* In attempting to prevent or treat these reactions the anesthetist may believe it necessary to add more and more Pentothal until dangerous degrees of depression result. To combat this pharmacologic weakness, the analgesic action of nitrous oxide is often used in a complementary fashion, as has been described.

It should be recognized that Pentothal cannot produce muscular flaccidity with any degree of safety. If Pentothal or Pentothal and nitrous oxide are selected for operations in which muscular relaxation is required, the addition of a curare compound is often essential. This is not without hazard, although in the

*We do not believe that Pentothal "sensitizes" the larynx, but merely fails to depress its normal irritability.

last few years substances have been developed which block conduction at the nerve muscle junction without lowering blood pressure. Nonetheless, profound degrees of respiratory depression in the postoperative period result occasionally from any of these substances. In our opinion their indiscriminate use will be followed by a higher mortality and morbidity.

5. Spinal Anesthesia. Spinal anesthesia, which produces superb muscular relaxation and affords ideal working conditions for the surgeon during intra-abdominal operations, exerts a profound effect upon the circulation. Two major physiologic alterations occur. There is a decrease in peripheral resistance as the result of interruption of vasoconstrictor impulses to arterioles. There is also a pooling of blood on the venous side of the circulation probably secondary to postarteriolar dilatation. As a result of either or both of these factors, venous return to the heart is diminished and cardiac output declines. Undoubtedly coronary blood flow is diminished. If the coronary vessels are sclerotic and are unable to adjust to this diminution in flow, coronary insufficiency may result.

On the other hand, it should be pointed out that during spinal anesthesia the heart is required to do less work because of the diminution in peripheral resistance and output. Thus, despite a reduction in coronary artery flow caused by the drop in blood pressure, there may be adequate oxygenation of the myocardium at the lower blood pressure since the heart requires less oxygen. The supply is less but the demand has also been reduced. This point deserves further investigation since, if proved correct, it may extend the use of spinal anesthesia.

6. Regional or Local Anesthesia. Superficially it might appear that isolation of a discrete area of the body by block of individual nerves with local anesthetic agents would disturb the general circulation least of all. Pain relief during operation could thus be obtained for the seriously ill individual without strain from the anesthesia. This stand must be qualified, however, for the following reasons. Intra-abdominal manipulation during block of the abdominal wall may, for example, be attended by a reflex decrease in blood pressure and by such unpleasant subjective reactions as pain, nausea, retching and dyspnea. The emotional upset involved is significant and supplemental general anesthesia is often required. If hypotension, therefore, has resulted either from traction or from absorption of excessive amounts of the local anesthetic, one's purpose in sparing the patient has been defeated since one has to resort in addition to general anesthesia. Epinephrine is frequently added to solutions of local anesthetic drugs to prolong the action of the latter. Epinephrine is a powerful cardiac stimulant and the increased amount of cardiac work resulting from its administration may be beyond the capacity of the coronary arteries to supply blood. Anginal pain or more serious evidences of coronary artery insufficiency may result. Such reactions are often erroneously interpreted as being due to the anesthetic agent. It is our opinion that local anesthesia is useful for operations on the extremities and body surface. Where less superficial operations are involved supplementation with Pentothal and nitrous oxide or cyclopropane is indicated to minimize hypotension and subjective discomfort.

II. Evaluation of the Patient

The patient with cardiac disease who is facing anesthesia and operation should be evaluated by three individuals: cardiologist, anesthesiologist and surgeon.

The cardiologist is best qualified to take a *complete* history, to make an *accurate* physical examination, and to *interpret* laboratory data and the results of special tests of the cardiovascular system. He can establish the pathologic diagnosis and can determine the degree of functional disturbance in each patient. He can decide whether the heart is in the best possible condition or whether further bed rest, the use of diuretics, coronary vasodilating drugs or digitalis would improve the patient's chances for a successful surgical convalescence.

We do not believe that the cardiac consultant should suggest the type or method of anesthesia if he is associated with a specialist in this latter field of medicine. Few cardiologists accompany their patients to the operating room, watch the problems of induction and maintenance, realize

the difficulties posed by the body habitus of the patient, or appreciate the requirements of individual surgeons. Until they have practical, first hand experience with the conduct of anesthesia, it is unwise for them to insist upon a particular course. If a cardiologist is asked to evaluate a patient for operation in a hospital where technician-anesthetists are employed, it is equally unwise for him to do more than suggest a plan of management. It is undoubtedly safer for the patient to receive that anesthetic agent with which the technician is most familiar than to have him attempt a *theoretically* safer procedure in which he is less skilled.

The anesthetist approaches the patient from a different standpoint. He must convince the patient that he is aware of the problem at hand, and is capable of managing it successfully. The apprehension of such patients is understandably acute. They must be reassured. The anesthetist studies the body habitus. He is concerned over the short, thick necked individual who snores readily. During the unconsciousness associated with general anesthesia such a person will suffer from respiratory obstruction unless carefully observed and treated. The obese patient with a large abdomen experiences a reduction of lung volume in the supine position as the diaphragm is pushed up. In such a patient, furthermore, spinal anesthesia may rise rapidly and to excessive levels. Previous experience with anesthesia is reviewed, as is previous experience with such drugs as morphine, Demerol, scopolamine. The number of pillows required by the patient when sleeping is of interest. It may also be advisable for the anesthetist to test in advance the patient's reaction to the position required for operation, for the circulatory abnormalities associated with the Trendelenburg or laterally flexed positions may be great.

The surgeon must assess the degree of muscular relaxation required, the estimated length of the procedure, the position desired. He must consider the necessity of limiting the extent of the operation because of the patient's reduced reserve. Fluid and electrolyte balance must be evaluated, together with the hazard of circulatory overload during intravenous fluid therapy. He must realize and accept the fact that the orthopneic patient may fare well in certain positions on the operating table.

III. Specific Disease Entities or Conditions

1. Pregnancy with Emphasis on Mitral Stenosis as a Complicating Factor. The circulation is considerably altered during pregnancy. At term cardiac output is increased by approximately 25 per cent, plasma volume by about 40 per cent. Of even greater interest is the effect of labor itself on the circulation. The variations in blood pressure are of greater magnitude than in any other clinical conditions which we have studied by intra-arterial pressure measurements. Pulse pressure may more than double within 10 seconds of the onset of a uterine contraction; a rise in systolic pressure of 60 to 80 mm. Hg is not uncommon. The least rise accompanies a uterine contraction which is not felt by the patient; a greater rise is noted during a contraction which the patient recognizes; the greatest hypertension follows a combination of uterine contractions and voluntary bearing down. The effect of this increased stress on the heart has obvious implications for the woman with a diminished cardiac reserve.

For two reasons we believe that spinal or caudal anesthesia may be useful for pregnant patients with cardiac disability, particularly if vaginal delivery is elected. The administration of any type of anesthesia tends to minimize the wide swings of blood pressure noted above but the smoothest curves have been achieved during spinal anesthesia. Under this method variations in blood pressure are reduced to alterations which cause little concern. This result should be the same during caudal anesthesia. The second reason involves the type of cardiac disease most frequently seen.

About 90 per cent of pregnant patients with cardiac disease have had rheumatic fever. The majority of valvular lesions are of the mitral valve. For those women who, during pregnancy, have experienced episodes of acute pulmonary edema often associated with hemoptysis, spinal or caudal anesthesia offers significant safeguards. Both methods produce a circulatory effect which might be termed a bloodless phle-

botomy. Vasomotor fibers to arterioles and venules are blocked in increasing numbers as the level of anesthesia rises. Venous pressure falls and blood is pooled in the periphery. This is of advantage to the patient with incipient pulmonary edema. Indeed, spinal anesthesia has been used in the treatment of pulmonary edema because of the circulatory adjustments produced.

The position of the patient is important. By definition the orthopneic patient cannot lie flat comfortably, and there are patients in whom pulmonary edema is precipitated by assumption of the supine position. It is strange how frequently this is overlooked in surgical practice. Particularly is this true when general anesthesia is administered and the patient cannot complain vocally of dyspnea. The semi-Fowler position with the head and chest elevated is essential for individuals with incipient heart failure. This is all the more important when cardiac weakness is combined with the elevated diaphragm and respiratory embarrassment of a full-term pregnancy.

For less seriously ill patients, nitrous oxide anesthesia together with various types of local block affords a useful combination.

2. Hypertension. Benign essential hypertension, almost regardless of the degree of elevation of blood pressure, causes relatively little concern to the anesthesiologist. If symptom free and particularly if the hypertension has persisted for years, these patients go through anesthesia and operation exceedingly well. It is only when the elevated blood pressure is associated with obvious damage to the heart, kidneys or cerebral circulation that such patients cause concern. Even under these circumstances it is surprising how well such patients withstand the stress of operation. Extensive sympathectomy and/or adrenalectomy have recently offered the anesthesiologist the opportunity of anesthetizing many seriously ill patients whose hypertension is complicated in a variety of ways. This experience has strengthened the belief that patients whose physical examination and laboratory data are discouraging indeed, may nevertheless pass through surgical procedures successfully.

Our original approach to patients whose hypertension was complicated by cardiac, cerebral or renal damage was based more on logic than on experimental evidence. It appeared reasonable to assume that if the hypertensive individual's chief problem was that of previous congestive failure, one was justified in permitting mean arterial pressure to decline somewhat during anesthesia and operation rather than to attempt to maintain it at preoperative levels by excessive intravenous fluid therapy or use of vasopressor substances, both of which might overtax the weakened myocardium. If, on the other hand, the patient's history suggested that the primary weakness was in cerebral or renal tissues, an effort was made to maintain an adequate blood pressure during operation, even if this involved a constant infusion of such a drug as, Neosynephrin, norepinephrine or the like. General anesthesia was used for all patients. Efforts were made to avoid excitement during the induction of anesthesia, although it was interesting that when arterial pressure measurements were made continuously even during relatively strenuous bouts of excitement, systolic blood pressures rarely rose more than 30 mm. Hg. Induction with sodium thiopental was not infrequently used in an attempt to put the patient to sleep as quietly as possible. Maintenance was then carried on, usually with ethyl ether. As long as the patient continued to be warm and dry, parenteral fluid therapy with glucose in water (rather than saline) or whole blood was continued cautiously. If the skin became cold, clammy or dusky, with peripheral vasoconstriction evident, the rate of infusion was increased significantly and a pressor drug whose primary action was central rather than peripheral was employed, for example, ephedrine. It has seemed logical to believe that if reflex peripheral constriction in response to hypotension were already maximal there was little indication for a drug whose primary site of action was peripheral. Perhaps this was fallacious.

The most recent change in attitude towards the anesthetic management of patients with hypertension (and actually other patients as well) is the concept of deliberately produced

and controlled hypotension. Though still unsettled, the arguments involved are of great interest to internists.

During the past several decades various individuals have suggested that a decrease in the blood pressure of a patient undergoing an operation may not be hazardous, but may even be useful, particularly from the viewpoint of minimizing blood loss and decreasing thereby the operative time. For example, neurosurgeons were not averse to permitting a decline in blood pressure during difficult craniotomies in order to obtain hemostasis.

Recently a number of workers have reopened the question. Gillies, in Scotland, has administered spinal anesthesia, avoiding the prophylactic injection of a pressor drug, and has attempted to produce a relatively bloodless operating field by a deliberate reduction in blood pressure. The metabolism of the patient is lowered by a minimal degree of general anesthesia. Oxygen is administered in concentrations above that in room air, and the patient is placed in such a position as to pool blood in the lower extremities. Goffen and colleagues, in this country, have used epidural anesthesia for the same purpose, as part of the anesthetic management of patients undergoing a fenestration. Gardner, Hale and others have developed a technic of controlled arterial bleeding, with provision for immediate reinfusion of the blood decreasing the hazard of the procedure. Drugs which depress the circulation directly have also been administered purposely during operation, hexamethonium bromide being the drug used most often.

Under what circumstances is such an approach justified? As already pointed out, one tends to worry much less about hypotension if the patient's skin is warm, dry and of good color, if the pulse is full, of reasonable rate and if there is a reasonable pulse pressure. If the patient is conscious, the presence of mental acuity, the absence of restlessness, anxiety, air hunger, chest or arm pain taken together suggest adequate cerebral and coronary blood flow. These functions are more difficult to evaluate in the unconscious patient. One can readily admit to having observed patients whose absolute level of blood pressure has been as low as 70 mm. Hg systolic but who have appeared to be otherwise in good condition. One must also admit, however, that other patients with similar levels of blood pressure have experienced lesions of the brain, heart, liver or kidneys due either to an inadequate flow of blood through patent vessels, or to an actual occlusion of vessels by thrombosis or spasm. It is perhaps difficult to prove that the low blood pressure *caused* the complications, but the burden of proof is on those who deny the likelihood.

All of the factors which determine whether the body can tolerate hypotension are not known, but the following must be of significance:

a. The duration of the hypotension.

b. The degree of the hypotension.

c. The previous condition of blood vessels, particularly those supplying the heart, brain, kidneys and liver. If these vessels are sclerotic or otherwise abnormal, changes in their caliber in response to hypotension may not occur as readily as with normal vessels, and an insufficiency of blood may result.

d. The metabolic needs of the tissues during hypotension, again with particular emphasis on the heart and brain. The lower the metabolism, the greater the reduction in supply of blood which can be tolerated. Thus, the cellular depression associated with general anesthesia may be a relative safeguard during periods of low blood pressure, since the tissue requirements are presumably lowered at the same time. Likewise, if the hypotension be produced by spinal anesthesia, the heart may be better protected than one might imagine at first glance, because it is being called on to do less work against the lessened peripheral resistance. The coronary blood supply may be curtailed, but so may the demand for this blood.

e. The liberation of specific depressant substances from ischemic tissues. Shorr's demonstration that a vasodepressor material may be formed in the liver of shocked animals, or a liver subjected to poor blood flow, has widespread implications. This may only be the first of a group of toxic products so formed, the

impact of which on the body as a whole may be serious.

The successful use of deliberately produced arterial hypotension will depend entirely on whether tissue nutrition to the heart, brain and liver can be maintained during the period of low blood pressure. The kidney apparently will survive reasonable insults. The clinician electing this procedure must therefore be able to predict which patient will tolerate it. Most investigators will agree that young, healthy subjects will withstand reduced blood pressure satisfactorily. Most will agree that aged, sclerotic subjects with previous histories of coronary, cerebral or renal insufficiency will constitute poor candidates. Who, however, can safely select the patient midway between these two extremes?

3. Coronary Artery Disease. There is no single satisfactory approach to the anesthetic management of the patient with coronary artery disease, particularly if an intra-abdominal operation is planned. The following suggestions are recommended:

a. Assurance through personal contact that the anesthetist is aware of the patient's particular problem. This relieves a great source of anxiety on the part of the patient who frequently worries lest those concerned with his care be not completely familiar with his cardiac disability.

b. Adequate sedation prior to operation. The mental stress of a trip to the operating room is understandable and attacks of angina pectoris or coronary insufficiency may be precipitated by such an emotional crisis if proper sedation has not been achieved.

c. Smooth induction of anesthesia. A stormy induction with the likelihood of struggling, respiratory obstruction, anoxia, and retention of carbon dioxide is hazardous for a heart whose blood supply is marginal. Since this blood supply in all probability cannot be increased in the normal fashion by coronary artery dilation, further demand for blood secondary to increased cardiac work should be avoided.

d. Maintenance of blood pressure. A reduction in mean arterial pressure will reduce the amount of blood flowing through the coronary arteries. Although, during hypotension, cardiac work may be reduced, since the heart will be opposing less peripheral resistance, one cannot be certain that the demand for nutrients will be sufficiently lowered to be satisfied by the decreased supply.

e. Administration of oxygen. The value of this is self-evident.

Regional anesthesia is thought by some to be the safest form of pain relief for these patients. If an intra-abdominal operation is planned, we prefer general anesthesia with ether or cyclopropane to unsupplemented regional anesthesia for several reasons. Under local anesthesia the patient is conscious and aware of the sight, sounds and smells of an operating room. This is not calculated to provide mental calm unless large amounts of sedatives are provided. Furthermore, despite satisfactory anesthesia of the abdominal wall, intra-abdominal manipulations are often accompanied by severe pain, nausea, vomiting, dyspnea and a lowered blood pressure. These signs and symptoms are the result of traction reflexes and are noted as intraperitoneal structures are placed under tension with grasping forceps or retractors. The sequence of events is poorly understood, although the fall in blood pressure has been ascribed to a reflex constriction of the portal venous system with diminished venous return to the heart and a lowered cardiac output. The pain, frequently substernal, and the subjective feeling of shortness of breath have been attributed to a reflex reduction in coronary blood flow, although evidence on this point is not conclusive.

If there is virtue in urging the patient with coronary artery disease to live quietly, avoid stress and strain, and adjust his ways to a calmer existence, it seems unwise to subject this same individual to the mental and physical upset occasioned by an operation performed under local anesthesia, when a properly administered general anesthetic can abolish the mental disquiet and minimize the untoward effect of intra-abdominal traction.

4. Congestive Heart Failure. In our experience surgical emergencies have been rare in patients during acute episodes of congestive heart failure. Regional anesthesia has been employed in the few instances requiring immediate opera-

tive intervention. The patient has been kept with the head and thorax elevated. If oxygen therapy has been required prior to operation, this is continued during the surgical procedure. No parenteral fluid therapy is given. Venous tourniquets and a slow intravenous drip of theophylline ethylenediamine may be indicated in the presence of impending or actual pulmonary edema. Theoretically, the hemodynamic effect of spinal anesthesia suggests this method of pain relief in such patients. We have administered spinal anesthesia to patients with acute pulmonary edema as the result of sudden overloading of the circulation with intravenous fluid therapy. The results have been difficult to evaluate, however. If an elevated central venous pressure is needed to maintain cardiac output in certain patients, this reasoning may be incorrect.

5. Congenital Heart Disease. Because of the increase in the number of congenital abnormalities being studied by surgeons, a discussion of all of the problems involved in these patients would be too lengthy for this paper. Suffice it to say that most patients with a patent ductus arteriosus, tetralogy of Fallot, or coarctation of the aorta withstand anesthesia and operation exceptionally well. Since many of the surgical approaches to these diseases involve direct manipulations of the heart, we shall present some discussion of the utility of cardiac depressant drugs in the next section.

IV. Cardiac Arrhythmias during Anesthesia and Operation

Disorders of cardiac rate or rhythm are not infrequent in the anesthetized patient. There are certain circumstances under which one anticipates such abnormalities. Direct laryngoscopy and the introduction of a tube into the trachea is almost always followed by a rise in blood pressure and tachycardia. These changes may be marked if the depth of anesthesia is minimal. Manipulations near the hilum of the lung, stripping of an adherent pericardium, direct approaches to the heart chambers may all be accompanied by gross irregularities. Occasionally arrhythmias appear to occur "spontaneously."

Some of the mechanisms responsible for such occurrences have been considered in the section on cyclopropane. Those incident to increased vagal activity (occasionally sufficient to cause cardiac standstill) are best treated by atropine administered in large doses intravenously. As a rule their clinical importance is less than disorders indicative of increased myocardial irritability. Under these conditions the anesthetic agent itself appears to have set the stage. The trigger may take the form of increased circulating epinephrine following direct injection, surgical manipulation or because of carbon dioxide accumulation or anoxia. Ectopic foci appear and gross disorders of rhythm result.

The prevention of these arrhythmias is based logically on the preceding information. Direct laryngoscopy and intubation of the trachea should be carried out under reasonably deep planes of anesthesia. Circulatory alterations are minimized under these conditions. Adequate ventilation throughout the period of induction and maintenance is essential. Not only must the hemoglobin be well oxygenated and the patient be of good color but the more insidious and the more difficult to recognize accumulation of carbon dioxide must be prevented. Recent work indicates that respiratory acidosis may be the common accompaniment of anesthesia for major operative procedures, both in the abdomen and in the chest. Since ventricular rhythms are increased in incidence and severity in the presence of carbon dioxide accumulation, prevention of this physiologic abnormality is the obvious answer. The injection of all sympathomimetic amines should be prohibited unless absolutely essential. If the need is great, neosynephrine or methoxamine should be used. These are not associated with the production of ventricular arrhythmias.

One then comes to a discussion of the use of drugs specifically designed to depress cardiac irritability by a direct action on the heart or intended to minimize cardiac abnormalities by blocking sympathetic inflow to the heart. The group of cardiac depressants most commonly used includes three substances: quinidine, procaine and procaine amide. All three of these can be given intravenously and two, quinidine and procaine amide, can be given by mouth.

Their pharmacologic action is intricate and complex.

As a generality, it is safe to say that the beneficial results following the action of any of these drugs depend upon a general cardiac depression. In this very action, of course, lies the possibility of harm. All three drugs can cause serious degrees of hypotension. All can produce flabby, dilated hearts if the dose is excessive and all can produce ectopic foci in the ventricles, the most severe and serious manifestation of which is ventricular fibrillation. They are undoubtedly of real use clinically but the dosage needed to provide protection and to avoid any of the toxic reactions is difficult to predict in advance. A great deal remains to be learned about their ultimate role.

The substances which block out or reduce the effect of sympathetic activity on the heart include ethyl ether and Dibenamine. As already indicated ether is almost always given with cyclopropane, small amounts of the former serving to produce the type of "functional decerebration" which appears to cut the heart off from impulses arising from the sympathetic center in the hypothalamus. Both ether and Dibenamine can be shown to reduce the incidence and severity of ventricular rhythms arising as a result of cyclopropane anesthesia. How useful they may be in minimizing other disorders of rhythm is less certain.

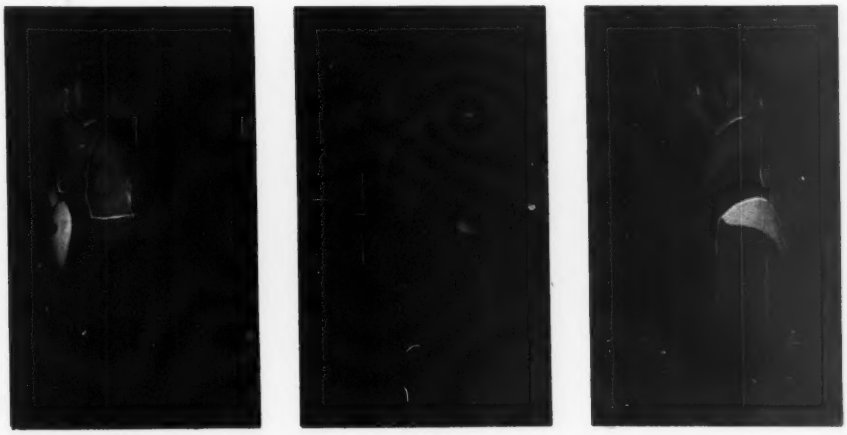
To illustrate the way in which an anesthesiologist faces the problem of arrhythmia, one can outline the regime employed when a multifocal ventricular tachycardia develops during anesthesia. Since these rhythms are more likely to occur under deep anesthesia, the anesthetic concentration is reduced. Since they may result from inadequate ventilation, every attempt is made to insure adequate oxygenation and removal of carbon dioxide. If ether had not been added, a small amount is usually administered. If none of these measures is successful, one of the cardiac depressant substances may be injected intravenously. Either quinidine lactate, procaine hydrochloride or procaine amide may be administered in doses of from 50 to 100 mg. per injection. Such an injection may be repeated several times. In the majority of instances these measures suffice. Less commonly, ventricular tachycardia may continue only to stop abruptly for no apparent reason. Clinical experience indicates that the great majority of such patients show no abnormality during anesthesia, operation or the postoperative period which indicates that their circulatory system had been seriously taxed. One dislikes seeing such abnormalities of rate and rhythm but one learns to live with them, in a sense, in the belief that ultimate damage will be minimal.

It is unfortunate that anesthesiologists do not know more about cardiology and that cardiologists do not have time to spend in the operating room. A great deal could be learned about cardiac arrhythmias, their mechanisms, significance, prevention and treatment if these two groups of medical specialists were to pool their information.

V. Conclusion

Teamwork between cardiologists, surgeons and anesthesiologists has increased the likelihood of survival of patients whose surgical disease is complicated by decreased cardiac reserve. Two main fields should be further explored if the reduction in mortality and morbidity is to continue. More must be learned of the basic actions of anesthetic agents and technics on the circulation of man. Greater efforts should be made to collect and analyze data on the actual course of patients with heart disease anesthetized in different ways and subjected to different operations.

American Heart Association Heart Models in Health and Disease



MODEL 5. Marked Mitral Stenosis

A NEW series of latex rubber models of normal and abnormal hearts have been prepared for the American Heart Association by Abram Belskie, the noted medical sculptor. The present set consists of 10 different models.

To the beginner in cardiac roentgenology, there is a bewildering difference between the configuration and relative positions of the heart chambers before and after removal of the heart from the body. To help obviate this difficulty it was thought worthwhile to construct in permanent form this series of life-size hearts, normal and diseased. These real models have the outlines of the main coronary blood vessels and the reflections of the pericardium shown on the surface. Each model can be fitted into a base which is a model of the diaphragm in a sthenic individual. A number appearing on each model identifies it.

These models are delivered in the natural color of latex rubber. They may be painted in a number of ways. The color plate shows model 5 (marked mitral stenosis), which has been painted with fluorescent pigments; the photographs were taken under ultraviolet light. This type of paint may be obtained from:

J. Everett Nestell, 71 Murray Street, New York City

Sweitzer Brothers, Cleveland, Ohio

Stroblite Company, 35 West 52 Street, New York City

The models may be painted with any type of paint or water color which will adhere to a rubber base.

These models may be obtained from the American Heart Association, 1775 Broadway, New York 19, New York. The price of a complete set of ten models with one diaphragm base is $150.00. Single models with a diaphragm base cost $22.50 and single models without the diaphragm base are $16.50. The models are delivered in the natural color of latex rubber. Packing and shipping costs are extra.

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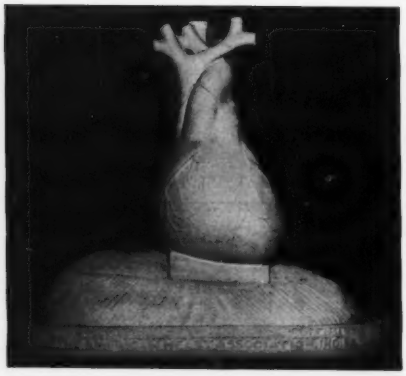
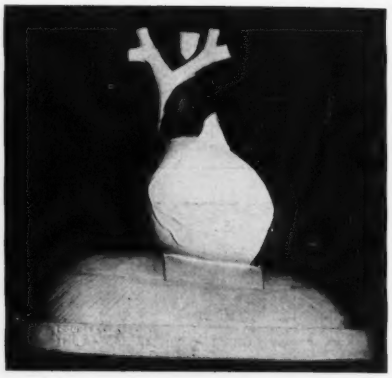


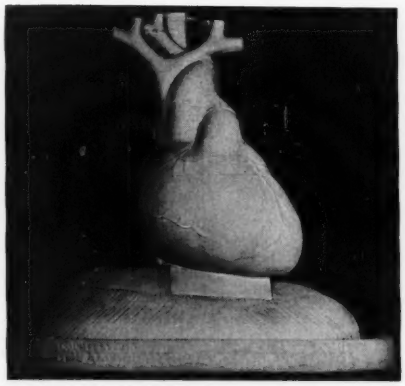
MODEL 1. *Average normal heart.* The appearance of the cardiac shadow is influenced by the position it occupies in relation to the diaphragm. Between the extremes of the horizontal (Model 2) and vertical (Model 3) shaped hearts is the oblique shape seen in the sthenic (average) individual. The correct positions of the esophagus and trachea are shown. The convexity of the right heart border is formed by the right auricle below and the ascending aorta above. The apex of the heart is formed entirely by the left ventricle and the convexities on the left border are formed by the aortic knob, the pulmonary artery and the left ventricle from above downward.



MODEL 2. *Transverse type of heart* (model painted in this photograph). The axis in this type of heart is approximately at right angles to the great vessels, producing what is known as a "transverse heart." The individual is usually thick-chested, short, obese (hypersthenic), with the heart lying horizontally on a high diaphragm and the apex extending well to the left. The transverse diameters of heart and vascular pedicle are increased.

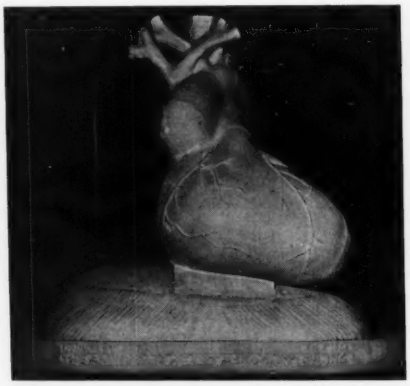
MODEL 3. *Vertical type of heart* (model painted in this photograph). The longitudinal axis in this type of heart closely approaches a vertical position. It is seen in thin persons with a long, narrow chest—the asthenic habitus. The transverse diameters of the heart and the vascular pedicle are both reduced. The diaphragm is low in position and the convexity of all contours in all views is only slightly prominent. The contour of the pulmonary artery forms a large part of the left border below the aortic knob. The arch of the aorta appears short in the left anterior oblique view and is curved on a small radius.

MODEL 4. *Moderate mitral stenosis.* In the anterior view there is a straightening of the left heart border, owing to prominence of the pulmonary artery. There is a moderate degree of dilatation of the pulmonary artery. In the right anterior oblique view, definite enlargement of the left auricle is observed. The retrocardiac space is diminished, especially in its upper and middle thirds, and the esophagus is slightly displaced to the right. There is no elevation of the main bronchus in the left anterior oblique view.



MODEL 5. *Marked mitral stenosis* (see color plate). The left auricular enlargement has progressed further, causing convexity on the midportion of the left heart border by the dilated pulmonary artery. In the anterior view the left auricle can be seen on the right border of the heart, projecting above and behind the right auricle. The enlargement of the left auricle has largely obliterated the upper two-thirds of the retrocardiac space in the right anterior oblique view and has displaced the esophagus posteriorly. The angle of bifurcation of the trachea and its left main branch is elevated, which is best seen in the left anterior oblique view. There is moderate dilatation and prominence of the right ventricle and right auricle.

MODEL 6. *Mitral stenosis and aortic insufficiency.* In addition to the findings of mitral stenosis as described above in Model 5, there is also, in this case, marked left ventricular enlargement, due to the presence of aortic insufficiency. This combination often results in an extremely large heart. In the left anterior oblique view it will be seen that the lower third of the retrocardiac space is largely obliterated by the enlargement of the left ventricle.



MODEL 7. *Aneurysm of the ascending aorta and aortic insufficiency.* In the anterior view the aneurysm can be seen on the ascending limb of the aorta. Since there is insufficiency of the aortic valve, there is also enlargement of the left ventricle. The aneurysm projects to the right beyond the right margin of the superior vena cava, which it displaces posteriorly and to the right. The aortic knob is blunt, presenting a marked convexity on the upper left border of the vascular pedicle. The trachea and esophagus are displaced posteriorly and the latter is compressed against the vertebral column.

MODEL 8. *Cast of the chambers of the heart and great vessels.* This model was devised primarily to facilitate the understanding of angiocardiography. The venae cavae, the right heart and the pulmonary artery are detachable as a unit. The chambers in this model correspond to those which would be present in Model 1 if they could be visualized.

MODEL 9. *Hypertensive heart and tortuous arteriosclerotic aorta.* This model illustrates the enlargement of the left ventricle seen in hypertension, with widening and tortuosity of the whole aorta. In the anterior view, the ascending limb projects to the right of the superior vena cava, while the arch runs obliquely posteriorly to the left instead of almost directly posteriorly. The aortic knob is accentuated and the whole arch takes a wide swing, owing to lengthening of the aorta.

MODEL 10. *Cor pulmonale.* The nature of the deformity of the heart in long-standing lung disease is illustrated in this model. The effects are upon the right ventricle and pulmonary arterial trunk. In the anterior view the pulmonary artery is prominent and increased in width; it projects to the left to form a marked convexity on the left heart border. In the lateral view the anterior border of the heart presents a marked prominence in the region of the pulmonary artery.

ABSTRACTS

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Abstracters

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BLOOD COAGULATION

Stefanini, M.: Autocatalytic Formation of Thrombin in Blood Coagulation. Acta med. scandinav. **140:** 290 (Aug.), 1951.

The process of coagulation of the blood is divided into (1) a slow phase during which enough thrombin is formed to set the autocatalytic mechanisms in motion, and (2) an accelerated phase in which thrombin is formed in increasing amounts and at a progressively more rapid rate so that fibrinogen is massively converted to fibrin. The autocatalysis which is set in motion by the thrombin is thought to be carried out by the aggregation and lysis of platelets by thrombin, with ever increasing activation of thromboplastin and finally increased formation of thrombin, and the formation of a powerful accelerator found in serum through the action of thrombin or plasma prothrombin conversion factor (PPCF) or other plasma precursors. Prothrombin, thromboplastin and calcium react then in the presence of serum and platelet accelerator to form thrombin in increasingly larger amounts. Finally enough thrombin is formed to clot enough fibrinogen to assure the formation of a solid clot.

The author believes that in order to prevent this chain reaction mechanism from excessive extension of the thrombus along the vascular tree, there must exist a control mechanism. This is considered to consist primarily of the adsorption of the thrombin on the fibrin clot and its gradual neutralization by natural antithrombin as the thrombin is slowly released at the time of retraction of the clot.

ROSENBAUM

Mueller, J. F., Ratnoff, O., and Heinle, R. W.: Observations on the Characteristics of an Unusual Circulating Anticoagulant. J. Lab. & Clin. Med **38:** 254 (Aug.), 1951.

A case is reported of a patient with subacute bacterial endocarditis whose plasma contained an unusual anticoagulant. At 25 C., the clotting time of the patient's blood was greatly prolonged, while at 37 C. it was usually within normal limits. Small amounts of the patient's whole blood delayed the clotting time of normal blood at 25 C. but not at 37 C. In the absence of the formed elements of the blood, the circulating anticoagulant was active at both temperatures. It did not inhibit the action of thrombin nor did it appear to inactivate either fibrinogen or prothrombin.

The fact that the formed elements of the blood were able to counteract the action of the anticoagulant at 37 C. was explained on the basis that at this temperature there was a release of potent thromboplastic material from such cells as the leukocytes and platelets.

ABRAMSON

Apul-Haj, S. K., Watson, J., Rinehart, J. F. and Page, E. W.: The Thromboplastic Activity of Hyaluronate. Science **114:** 237 (Aug. 31), 1951.

Hyaluronate, a mucopolysaccharide, was investigated with regard to a possible thromboplastic activity. It was found that the material had a greater effect on the coagulation time than that produced by an equivalent amount of beef lung thromboplastin. Similar results were obtained when hyaluronate was tested against brain thromboplastin in the one-stage prothrombin method. It was further noted that calcium was essential for hyaluronate activiy and that the rate of prothrombin conversion was considerably increased by the presence of the accelerator factor.

The authors conclude that sulfate-free hyaluronate, as it occurs naturally in the body, perhaps in combination with a protein, is an active thromboplastic agent, this function being related to its viscosity. Unlike tissue extracts, its activity is destroyed by hyaluronidase or by any physical procedure resulting in depolymerization.

ABRAMSON

Duff, I. F., Linman, J. W., and Birch, R.: The Administration of Heparin. Surg., Gynec. & Obst. **93:** 343 (Sept.) 1951.

The authors review the indications and contraindications for the use of heparin and compare the reactions to this drug with those obtained with dicumarol.

Heparin should be used with caution, if at all, in the presence of threatened abortions, potential hemorrhagic diathesis, increased capillary fragility, suspected intracranial hemorrhage, and actual or potential bleeding from inaccessible ulcerative lesions, particularly of the gastrointestinal tract. With caution, it may sometimes be employed when dicumarol is contraindicated, as for example, in advanced age, severe liver disease, congestive heart failure, severe alkalosis or acidosis, and in the nursing mother. It should also be used in preference to dicumarol when adequate laboratory facilities are not available for daily prothrombin determinations. Furthermore, in the full evaluation of the relative worth of the two drugs, it must be considered that the incidence of bleeding associated with heparin is considerably less than with dicumarol.

The effect of heparin on the clotting time is measured by the simple Lee-White test, and adequate therapeutic effect being prolongation of the time to twice the pretreatment figure. When the drug is given intravenously in full strength the test can be omitted. However, when depository heparin is used, appropriately spaced clotting time determinations should be done.

ABRAMSON

CONGENITAL ANOMALIES

Soulié, P., Joly, F. Carlotti, J., and Sicot, J.-R.: A Comparative Study of the Hemodynamics in Tetralogy and Trilogy of Fallot. (A Study of 43 Cases). Arch. mal. coeur **44:** 577 (July), 1951.

The clinical symptomatology of Fallot's trilogy (pulmonic stenosis with interatrial septal defect) and the classic tetralogy are similar and their distinction difficult. In order to establish differential diagnostic criteria, the authors studied 22 cases of tetralogy and 21 cases of trilogy by cardiac catheterization and angiocardiography.

A constant finding in common cases of tetralogy is an equal pressure in the right ventricle and in the aorta. In the trilogy, the principal and almost pathognomonic sign is marked hypertension within the right ventricle, with systolic values which may exceed those found in the systemic circulation. The pressure in the pulmonary artery may be normal in the trilogy but is always low in the tetralogy. The intraventricular shunt in the tetralogy is large and predominantly right to left, and is effected mainly through the intraventricular defect and, less frequently, over the over-riding aorta. Consequently, the systemic output is high, while the pulmonary flow is decreased. In the trilogy, a right to left shunt occurs in the auricles through the communication in the septum and both systemic and pulmonary flow are usually low. The amount of shunted blood in cyanotic instances of trilogy does not exceed 50 per cent of the systemic flow and may decrease on exercise in cases without cyanosis.

In a third of cases with tetralogy and in more than half of the trilogies, it was not possible to prove the communication between the right and left cavities by cardiac catheterization. On the other hand, the diagnosis of an over-riding aorta depends entirely on the latter procedure, that is, insertion of the catheter into the aortic lumen. The angiocardiographic signs are not conclusive, since early filling of the vessel may also be seen in the presence of an interatrial septal defect.

PICK

Joly, Fr., Carlotti, J., and Sicot, J. R.: Intraventricular Communications (Diagnosis by Catheterization). Clinical and Physiologic Study. Arch. mal. coeur **44:** 602 (July), 1951.

The authors studied 21 cases with intraventricular septal defect, all proved by cardiac catheterization and two by autopsy. The subjects were divided into three groups according to clinical, roentgenologic and electrocardiographic findings. The first group, with the typical murmur, a heart of normal size and without axis deviation in the electrocardiogram, was considered to represent the classical Roger's disease. In a second group, the murmur was found sometimes at a higher level than usual or was absent. The heart was enlarged with expansive pulsations of the pulmonary arterial tree and the electrocardiogram showed right axis deviation or right bundle branch block. The authors termed these cases intraventricular communications with dilatation of the pulmonary artery. The third group, roentgenologically similar to the second, but with the acoustic phenomena similar to that of patent ductus arteriosus and with an electrocardiogram of "combined heart strain," was considered to be complicated by aortic regurgitation. Angiocardiography revealed delayed opacification of the aorta in all three groups. With cardiac catheterization, the pulmonary pressure was found normal in Roger's type and was elevated in the two other groups. A large left to right shunt could be demonstrated in most cases, and represented 25 to 50 per cent of the total pulmonary flow. The peripheral arterial saturation, as evidence of right to left shunt, was only slightly decreased even in "old"

cases and in cases with signs of marked increase in resistance of the pulmonary circulation.

The authors emphasize the difficulties in differentiating some cases of intraventricular septal defect from other types of congenital malformation with similar symptomatology. Laminar flow and incomplete mixture of the blood, shunted from a left to a right cavity, may obscure the actual localization of the intracardiac communication. Thus, an intraventricular septal defect, associated with an enlarged pulmonary artery, may easily be mistaken for an intra-atrial septal defect; a patent ductus arteriosus or for Eisenmenger's complex without cyanosis.

PICK

Emery, J. L., and Illingworth, R. S.: Congenital Mitral Stenosis. Arch. Dis. Childhood **26:** 304 (Aug.), 1951.

Two cases of congenital mitral stenosis in infants 3 and 1½ years of age are presented by the authors. One was treated for four months as a right basal pleural effusion and had no cardiac murmurs at any stage. The clinical diagnosis was then changed to one of congestive heart failure of unknown etiology. The second presented bronchopneumonia superimposed on congestive heart failure and the characteristic murmur was found. Death in each case was due to congestive heart failure. The lesions in the heart appeared to be congenital in origin and due to abnormal development after the cavities of the heart had been fully formed. No evidence of fetal endocarditis or of a rheumatic process could be found.

BERNSTEIN

Adams, F. H., and Cunningham, S. C.: Fragility of Red Blood Cells from Newborn Infants and Children with Cyanotic Congenital Heart Disease. Pediat. **39:** 180 (Aug.), 1951.

Using the spectrophotometric technic, the authors studied the red blood cell fragility in newborn infants and in children with cyanotic congenital heart disease. The arterial oxygen saturations of the children with congenital heart disease ranged from 15 to 75 per cent. The blood from the majority of the subjects with congenital heart disease had a slightly greater fragility than the normal controls. The erythrocytes from the cyanotic patients were oxygenated but the fragility of the cells was still greater than the normal controls. Cord blood from the newborn was tested in a similar manner. An occasional specimen showed a slight increase in fragility. A marked spontaneous hemolysis of oxalated fetal blood was not observed by the authors.

MARGOLIES

Hahn, R. C., Edwards, J. W., and DuShane, J. W.: Coarctation of the Aorta as a Cause of Death in Early Infancy. Pediatrics **8:** 192 (Aug.), 1951.

The authors report on three cases of coarctation of the aorta in infancy at the level of the closed or closing ductus arteriosus. All three died of left ventricular failure which was probably secondary to the obstructive hypertension. At autopsy it was found that the collateral channels were poorly developed. It is pointed out that the development of collateral channels depends on the relation of the coarctation to the opening of the ductus arteriosus. The left ventricular output supplies the great vessels arising from the aortic arch in the normal fetus. The right ventricle, through the ductus arteriosus, supplies the major portion of the blood in the descending aorta. However, when there is a coarctation below the aortic mouth of the ductus arteriosus, both the left and right ventricles supply blood to the aorta proximal to the coarctation, and blood to the descending aorta arrives via collateral channels. If this did not take place there would be an insufficient blood supply to the placenta and the fetus would probably die prior to term. The authors, therefore, conclude that in coarctation distal to the ductus arteriosus, collateral circulation develops during fetal life and in such individuals the closure of the ductus after birth has no effect on the circulation. However, when the coarctation is proximal to the ductus, the same type of blood flow distribution takes place as in the normal fetus, and a collateral circulation does not develop prior to birth. With the coarctation at the level of the ductus arteriosus the authors believe that the development of collaterals depends on the direction of blood flow on leaving the ductus. With a flow directed proximal to the coarctation, collaterals are believed to develop, but when the flow goes into the descending aorta, an adequate collateral circulation does not develop, as in the three reported cases.

MARGOLIES

Scott, H. W., Jr., Elliot, S. R., II, and Clay, R. C.: Blood Volume in Congenital Cyanotic Heart Disease: Simultaneous Measurements with Evans Blue and Radioactive Phosphorus. Bull. Johns Hopkins Hosp. **89:** 121 (Aug.), 1951.

With the combined use of the Evans blue dye method for measuring plasma volume and the radioactive phosphorus method for direct measurement of red cell volume or whole blood volume, the authors studied 20 patients having congenital cyanotic heart disease and five noncyanotic convalescent adults. The patients with congenital heart disease had polycythemia and cyanosis due to a right to left intracardiac shunt with a diminished effective pulmonary blood flow. Studies revealed that these patients had a diminished plasma volume, an increased red cell volume and an elevated whole blood volume when compared with the noncyanotic group. Measurements done simultaneously with Evans blue and radiophosphorus in the 20 cyanotic patients showed the plasma volume to be reduced below normal by both the direct and the indirect methods. No studies were done on infants with congenital heart disease.

However, there was no significant differences between the volumes found in the cyanotic children and those of the cyanotic adults. The authors believe that this study suggests that maximal polycythemia and hypervolemia may be attained in midchildhood and that no significant alteration in the polycythemia pattern occurs after this period.

MARGOLIES

Nuboer, J. F.: Double Aortic Arch. J. Thoracic Surg. **22**: 208 (Aug.), 1951.

The author describes a case of congenital constriction of the trachea and esophagus, caused by a compressing double aortic arch in a male infant. From birth the child suffered from a distinct stridor. Respiration was easier when he was held erect. Filling the esophagus with barium revealed a considerable depression in the posterior wall near the third and fourth thoracic vertebrae. The trachea was also narrowed at this level. The correct diagnosis was then made and the patient was subjected to surgery. The ductus Botalli was resected and the anterior aortic arch was ligated and divided at the point of union with the posterior arch. When these steps were carried out, the esophagus and trachea were released from their stricture. The postoperative course was uneventful and all symptoms disappeared except for a slight stridor.

ABRAMSON

CONGESTIVE HEART FAILURE

Marvel, R. J., and Shullenberger, W. A.: Thromboembolic Phenomena Associated with Rapid Diuresis in the Treatment of Congestive Heart Failure. Am. Heart J. **42**: 194 (Aug.), 1951.

The authors studied 15 cases of congestive heart failure and two control cases to determine the effects of rapid dehydration on the blood coagulation system. The treated group consisted of 12 patients given digitoxin, sodium restriction, and mercurial diuretics, and three patients on the same regimen without digitoxin. Peripheral phlebothrombosis and pulmonary embolism occurred in three cases of the former group, and in one of the latter group. During rapid diuresis, hemoconcentration was the most consistent finding, accompanied by less consistent findings of increasing prothrombin values, elevated fibrinogen content, rapid coagulation time, and increased globulin fractions. These changes preceded the thromboembolic episodes, which occurred between the sixth and ninth days of therapy. The two control cases without heart disease were given mercurial diuretics, sodium restricted diets, and digitoxin. They developed no evidence of thromboembolic phenomena although they did have increases in the hematocrit levels, indicating hemoconcentration. The authors believe that rapid and marked diuresis plays an important role in the pathogenesis of thromboembolic complications encountered in patients being treated for congestive failure by producing hemoconcentration and increased viscosity of the blood. Prophylactic anticoagulant therapy would seem to be indicated in the dehydration period of selected cases of congestive failure.

HELLERSTEIN

CORONARY ARTERY DISEASE MYOCARDIAL INFARCTION

Fauteux, M.: Results of Surgical Treatment of Coronaritis. Arch. mal. coeur **44**: 637 (Aug.), 1951.

The author reports his experience in surgical treatment of 78 cases with coronary disease. The operation consisted in ligation of the great coronary vein and, in most of the cases, denervation of the coronary arteries. The technic of the operation and pre- and postoperative treatment are described.

Cases with typical angina, occurring on effort or at rest and resisting medical treatment, should be elected for surgical approach. Hypertension or healed myocardial infarction is no contraindication, but diabetes, even when treated adequately, is a bad operative risk. The operation is contraindicated in the presence of recent myocardial infarction and of bundle branch block.

Of the 78 cases treated by this method, two died on the operating table and 14 within 20 days following surgery. The mortality was larger (50 per cent) in cases over 60 years. The cause of death was pulmonary embolism in four cases, coronary thrombosis followed by ventricular fibrillation in two, and other complications in the remaining cases. Sixty-two cases survived up to 10 years, and in 45 the results are stated as excellent, good or improved.

PICK

Harman, J. B.: Angina in the Analgesic Limb. Brit. M. J. 4730: 521 (Sept. 1), 1951.

The author attempted to test the hypothesis proposed by Cohen that, in the case of angina pectoris, there is a continual stream of subliminal pain impulses from the heart and arm, which reaches a functionally related area in the sensorium. When integrated with the cortical pattern of the body image, the impulses are localized selectively in that segment. In eight patients with angina, a weak but extensive brachial plexus block was performed in order to produce an arm which was analgesic but which had power and other forms of sensibility only slightly affected. In each instance, the subjects were then walked over a test course until angina was experienced. In seven of the eight patients arm pain occurred after walking a much greater distance than the amount previously sufficient to elicit an attack.

However, in view of the fact that pain could still be elicited in the analgesic arm, the author concluded that hypothetical subliminal pain impulses could have played no part in producing the angina, since these must have been abolished by the blocking procedure.

ABRAMSON

Agress, C. M., Rosenburg, M. J., Binder, M. J., Schneiderman, A., and Clark, W. G.: Blood Volume Changes in Protracted Shock Resulting from Experimental Myocardial Infarction. Am. J. Physiol. **166:** 603 (Sept.), 1951.

Myocardial infarction was produced in open-chest dogs by embolization of the coronary arteries with plastic beads in methyl cellulose. Approximately 3 to 5 mg. per Kg. of beads produced widespread sublethal infarction. Evans blue (T-1824) blood volume studies carried out up to five hours showed a reduction in blood volume of 20 per cent over those of a control group.

OPPENHEIMER

Sayjen, J. J., Sheldon, W. F., Horwitz, O., Kuo, P. T., Peirce, G., Zinsser, H. F., and Mead, J., Jr.: Studies of Coronary Disease in the Experimental Animal. II. Polarographic Determinations of Local Oxygen Availability in the Dog's Left Ventricle during Coronary Occlusion and Pure Oxygen Breathing. J. Clin. Investigation **30:** 932 (Sept.), 1951.

The availability of oxygen in ischemic tissue of the dog's heart following coronary artery ligation was determined by a polarographic technic described by the authors. Platinum electrodes are inserted into the myocardium of the exposed heart. Subsequent determination of the precise location of the electrodes shows a differentiation into three zones. (1) A "central" area which shows a rapid decrease in available oxygen to less than a quarter of the control period values within a few minutes following ligation. The administration of pure oxygen by inhalation during coronary occlusion had no significant effect on the local oxygen availability in this area. (2) A "border" area which resembles the central area but shows a significant rise in local oxygen availability during oxygen breathing before termination of the occlusion. This supports the indication for inhalation of high oxygen concentrations in human myocardial infarction. (3) An "outside" area which shows no significant change on occlusion.

WAIFE

ELECTROCARDIOGRAPHY

Kroop, I. G., Steinberg, M. F., and Grishman, A.: The Nature of Left Axis Deviation in Congenital Cardiac Defects with Right Ventricular Hypertrophy. Am. Heart J. **41:** 891 (June), 1951.

The authors present electrocardiographic findings in three cases of interatrial septal defect with left axis deviation in the presence of right ventricular hypertrophy. Intrapulmonary artery potentials above the pulmonic valve were recorded by means of cardiac catheterization in these three patients, in two patients with tetralogy of Fallot, and in three patients with pulmonary heart disease. In patients with right ventricular hypertrophy, congenital and acquired, a characteristic rsR′s′ complex was recorded in the pulmonary artery just above the pulmonic valve. In normal hearts, the tall delayed R as seen in right ventricular hypertrophy was not present. The authors postulate that the recorded positivity (rsR′s′) above the pulmonic valve reflects the predominant potential of the hypertrophied right ventricle. In right ventricular hypertrophy, this potential may be reflected to the left arm, because of elevation and displacement of the pulmonary artery to the left secondary to hypertrophy. The reflection of this potential to the left arm (V_L) results in left axis deviation. The variability of the electrocardiographic findings in these patients with right ventricular hypertrophy indicates that rotation and cardiac position are more important than chamber hypertrophy alone in the determination of the extremity potentials and hence, the axis deviation.

HELLERSTEIN

Zatuchni, J.: The Electrocardiogram in Pregnancy and the Puerperium. Am. Heart J. **42:** 11 (July), 1951.

The author studied 25 normal patients with uncomplicated pregnancy, delivery and postpartum course, with the purpose of defining the position changes in terms of the mean electrical axis of the QRS and the electrocardiographic position, and, second, to determine whether there was any evidence of ventricular hypertrophy. Unipolar electrocardiograms were obtained on an average of 14 days before delivery, 11 hours after delivery, and also two to five days later. With advancing pregnancy, the mean electrical axis shifted to the left until the latter part of the third trimester, when it usually shifted toward the right. The shift to the right continued after delivery. The change in the mean electrical axis was more pronounced than in the electrocardiographic position as defined by Wilson and associates. The major positional change of the heart during pregnancy and the puerperium is rotation around its anteroposterior axis. There were no electrocardiographic manifestations of ventricular hypertrophy or "strain."

HELLERSTEIN

Evans, E., and Pohlman, L.: Complete Heart Block in Pregnant Women. Am. Heart J. **42:** 18 (July), 1951.

The authors present a case report of a pregnant 18 year old woman with complete heart block, probably congenital, and an interventricular septal defect. In the year before, the patient had completed her second pregnancy uneventfully. In the sixth week of her third pregnancy, hysterotomy and sterilization were performed because of the development of increased dyspnea on exertion, progressive enlargement of the heart, and primary T-wave changes in the electrocardiogram. The authors reviewed the literature and found 25 acceptable cases of complete heart block pregnancy. These patients survived pregnancy and fetal death was apparently rare. Termination of

pregnancy must be based on the usual indications, and not on the basis of the heart block per se.

HELLERSTEIN

Scherlis, L., and Grishman, A.: Spatial Vectorcardiography: Myocardial Infarction. V. Am. Heart J. **42**: 24 (July), 1951.

The authors studied the vectorcardiograms of 67 patients with evidence of myocardial infarction. In 41 patients, electrocardiographic evidence revealed infarction of the inferior aspect of the heart; in 16, the infarct was in the anteroseptal region; in 15, in the anterolateral area; in nine, in the anterior aspect; and in nine, presumptive infarction of the posterior aspect of the heart. Standard, unipolar extremity, precordial multiple thoracic leads, and, in 11 patients, esophageal electrocardiograms were recorded, in addition to simultaneously recorded frontal, sagittal, and horizontal plane vectorcardiograms. The orientation of the QRS sÊ loops after infarction depended upon the localization of the infarcted area. The loss of the electromotive forces due to destruction of tissue with resultant electrically inert areas alters both the electrocardiogram and the vectorcardiogram. The new resultant electromotive forces in infarction are due to the existence of a new analytic area which augments the electromotive forces of the diametrically opposite area because of the now unopposed potential in the uninvolved region. Spatial vectorcardiography as recorded by the authors' technic is considered to be a superior method for the analysis of the spatial distribution of the electromotive forces of accession in infarction.

HELLERSTEIN

Bunse, W., and Jahn, H.: Changes in the Electrocardiogram Caused by Anaphylactic Shock. Aerztl. Wchnschr. **6**: 755 (Aug.), 1951.

In a preceding paper, the authors reported that electrocardiographic changes during histamine shock are prevented by antihistaminic drugs. In the present paper, the effect of antihistaminics in anaphylactic shock is discussed. Rabbits were sensitized by hypodermic injection of 2 cc. of human serum and anaphylactic shock was provoked two to three weeks later by the intravenous injection of the same serum. In order to diminish the degree of the shock, all animals received 0.2 cc. per kilogram of Pernocton just prior to the second injection. Depression of the RS-T segments and flattening or inversion of the T-waves was observed in leads I and II during the state of shock in all control animals. Extrasystoles were rare. Prolongation of the auriculoventricular conduction time and 2:1 block were observed. An intravenous injection of antihistaminic drugs, administered before the shock was induced, did not prevent these electrocardiographic changes in two out of three rabbits. If only 1 cc. instead of 5 cc. of serum was used to induce the shock, the electrocardiographic changes mentioned above remained the same in eight animals, but in seven animals, normal electrocardiograms were registered. The authors conclude that antihistaminic drugs only partly influence the electrocardiographic changes during anaphylactic shock. Therefore, in addition to histamine, other histamine-like substances play a part in this condition.

SCHERF

Gordon, A., and Goldberg, H.: Correlation of the Electrocardiographic Pattern of Right Heart Strain and Evidence of Right Ventricular Hypertension in Congenital Heart Disease. Am. Heart J. **42**: 226 (Aug.), 1951.

The authors correlated cardiac catheterization data and the electrocardiographic patterns of 21 infants and children less than 15 years of age with right ventricular hypertension and congenital heart disease. Their criteria for right heart strain were based on the abnormal R/S ratio in V 4R and V 1. The R/S ratio at birth is normally infinity in V_{4R} and V_1; it then decreases gradually and approaches unity at about 3 years of age and is usually less than 1 thereafter. In 12 cases, when the pattern of right heart strain was present in the electrocardiogram, the right ventricular systolic pressure was elevated. In five cases, right ventricular systolic hypertension was present without the electrocardiographic pattern of right heart strain. In the remaining cases, the pattern of right heart strain was masked by patterns of left heart strain produced by other lesions, or aberrant coronary vessels. There was no specific correlation between the degree of hypertension and the amplitude of the QRS deflection or the R-S ratios in right heart strain patterns.

HELLERSTEIN

Dack, S., Corday, E., and Master, A. M.: The Heart in Acute Hemorrhage: A Clinical and Electrocardiographic Study. Am. Heart J. **42**: 161 (Aug.), 1951.

The authors studied 28 cases of acute hemorrhage in order to determine the factors which predispose individuals to coronary insufficiency, what its earliest clinical and electrocardiographic manifestations are, and the influence of therapy on this condition. The average age of the group was 49 years and one-half were over 50 years of age. An average of 1650 cc. of whole blood transfusion was given. In serial electrocardiograms, significant changes occurred in 85 per cent of the cases during the acute stage of hemorrhage. The changes generally involved the RS-T segment and T-wave and lasted from three hours to 30 days. During the recovery phase, there was a recurrence of abnormal T-wave alterations in 8 patients. In two patients with massive gastrointestinal hemorrhage, the pattern of myocardial infarction due to coronary occlusion occurred. The electrocardiographic changes were more marked. They appeared earlier, following lesser degrees of hemorrhage, in the older patients than in the younger, and lasted longer

in patients with antecedent heart disease. The hemoglobin level was a good guide to the severity of the electrocardiographic changes, although there were some exceptions. The electrocardiographic changes either preceded or followed the hemodynamic changes, the latter being more common. Clinical signs of coronary insufficiency (precordial or substernal pain) occurred in eight cases only. Signs of congestive heart failure were exhibited in five patients, three of whom had antecedent severe heart disease. Postmortem examination was performed in four cases, and in no instance was there evidence found of recent subendocardial necrosis.

The authors believe that the electrocardiographic changes following hemorrhage are due to an intrinsic change in the myocardium as a result of myocardial ischemia and anoxia, mainly of the deep layers. The authors stress the importance of prompt treatment of hemorrhage in patients with coronary or hypertensive heart disease.

HELLERSTEIN

Segers, M.: Auriculoventricular Synchronization and the Wolff-Parkinson-White Syndrome. Arch. mal. coeur **44:** 712 (Aug.), 1951.

The author presents clinical and experimental observations, which in his opinion support the concept of a hyperexcitable ventricular focus in the explanation of the Wolff-Parkinson-White syndrome. An electrocardiogram is shown with alternation of normal and anomalous conduction, in which ventricular premature beats had the same contour as the Wolff-Parkinson-White complexes. Corresponding observations were made in an experiment, in which a small area of the right ventricle of a rabbit was injected with strychnine. This was followed first by a period during which normal ventricular activation alternated with pre-excitation, and then by an idioventricular rhythm with ventricular complexes of the Wolff-Parkinson-White type.

In view of these observations and of previously described experiments, in which he demonstrated synchronization of rhythm of independent turtle hearts, being only in mechanical contact, the author believes that an accessory pathway between auricles and ventricles need not be implied to explain the ventricular pre-excitation in the Wolff-Parkinson-White syndrome. In the presence of a hyperexcitable focus in one of the ventricles, pre-excitation of the latter by the auricles may occur by mechanical or electrical stimulation, without any anatomic connection between the two chambers.

PICK

Robb, J. S.: Study of Bazett's K in Animals. Am J. Physiol. **166:** 584 (Sept.), 1951.

The author measured Q-T and cycle duration in eight species of animals and showed that Bazett's K ($Q\text{-}T = K\sqrt{\text{cycle}}$) may not be considered to be "Q-T corrected for heart rate," as K does not have a fixed arithmetic value. The fact that K is not an arithmetic constant does not prevent it from having considerable value. If the value of K and its trend is known, they may be of use in determining whether the myocardium is improving or deteriorating. Both rate and duration of systole are determined by a common fundamental condition of heart cells. Q-T or K and rate need not always change in a proportional manner or in the same direction. Strain raises K values above those expected at a given heart rate and increases in strain give still higher K values. In the agonal period, K decreases abruptly. The author is of the opinion that knowledge of K, compared with the expected value at any cycle length, gives more information than the Q-T measurement alone.

OPPENHEIMER

ENDOCRINE EFFECTS ON CIRCULATION

Blumgart, H. L., Friedberg, A. S., and Kurland, G. S.: Treatment of Incapacitated Euthyroid Cardiac Patients by Producing Hypothyroidism with Radioactive Iodine. New England J. Med. **245:** 83 (July), 1951.

The results of radioactive iodine therapy in 37 euthyroid patients with incapacitating chronic cardiac disease are reported by the authors. In 26 patients with angina pectoris, the results were excellent in seven, worthwhile in four, and not worthwhile in six. The follow-up period had been too brief for final clinical evaluation in the remaining nine. Of the 11 patients with congestive failure, worthwhile improvement was evident in four, unsatisfactory results in two, and a too brief period for evaluation in five cases. The authors feel that the over-all surgical mortality and the parathyroid and laryngeal complications militate against total thyroidectomy. The thiourea drugs are too irregular in action, they must be given for life and dangerous reactions may result from their use.

Although final indications and contraindications to radioactive iodine treatment have not been formulated, the authors include as unfavorable factors (a) rapidly progressive cardiovascular disease, including individuals in the terminal phases of their illness, (b) a basal metabolic rate of −15 per cent or lower, and (c) some associated conditions including rheumatic fever, bronchiectasis, emotional instability, atrophic cirrhosis, recent myocardial infarction and intermittent claudication. Patients who seem likely to benefit are those whose disease has been relatively stationary for one or more years, or who show evidence of appreciable cardiac reserve such as an ability to lose the signs of congestive failure, and persons who are tense and hyperactive. Approximately two-thirds of the patients developed mild to moderate transient thyroiditis. Management of the induced myxedema consists of maintaining the lowest

metabolic rate consistent with the patient's comfort by administration of small doses of thyroid.

ROSENBAUM

Govier, W. M., and Feenstra, E. S.: The Effect of Certain Hormones and Miscellaneous Compounds on Serum Disease in the Rabbit. Am. Heart J. **42:** 266 (Aug.), 1951.

Vascular disease was produced by the injection of horse serum in 229 rabbits and the effects of nitrogen mustard, various hormones and miscellaneous substances, believed to be concerned in allergic phenomena and cell-wall integrity, were studied by the authors. Nitrogen mustard was not effective. Adrenal cortical extract, ACTH and 17-OH-corticosterone were most effective in the prevention of lesions. Testosterone, thiamine triphosphate, and penicillin G (the latter in high dosage) were moderately effective. Tripelennamine, atropine, procaine, and sodium allyl mercaptoacetate (the precursor of penicillin O) did not prevent lesions.

HELLERSTEIN

Teilum, G., Engbaek, H. C., Harboe, N., and Simonsen, M.: Effects of Cortisone on Experimental Glomerulonephritis. J. Clin. Path. **4:** 301 (Aug.), 1951.

White rabbits of the same strain were immunized with a formaldehyde-killed Pfeiffer bacillus culture administered in intravenous injections three times weekly. The eight animals immunized for 7 to 16 months showed severe albuminuria. On biopsy of the renal tissue from the left upper pole of the kidney at laparotomy, five of these animals showed marked glomerular changes comparable with the natural disease (Ellis's type 1 and type 2 nephritis). Type 1 nephritis was characterized by proliferation of endothelial and epithelial cells of the tufts and also proliferation of extracapsular mesenchymal cells. The proliferating cells display pronounced pyroninophilia (with Unna-Pappenheim's methyl green-pyronine stain). In type 2 nephritis, the glomeruli are extremely poor in cells, with large deposits of a homogeneous substance in massive lumps.

The aforementioned five rabbits were administered cortisone hypodermically in daily doses of 20 mg. It was begun five days after the first operation and was given in series of six days' duration interrupted by one day on which another biopsy of the kidney was made. This was continued until the animal died. In rabbits showing type 1 glomerulonephritis, cortisone caused a marked regression of pyroninophilic cells inside and outside the glomeruli, and promoted a transition to homogeneous precipitates in the tufts and approached the picture of type 2 nephritis. In the case comparable to type 2 nephritis, further masses of homogeneous precipitates were accumulated in the tufts, whereas the cellular areas decreased. The histologic picture suggested amyloid nephrosis.

RINZLER

HYPERTENSION

Davis, L., Tarkington, J., and Anderson, R. K.: Physiologic Principles Underlying the Treatment of High Diastolic Hypertension by the Thiocyanates and Sympathectomy. Ann. Surg. **133:** 807 (June), 1951.

The effect of thiocyanate therapy was studied by the authors in a series of dogs made hypertensive with the Goldblatt clamp. A depletion of lipid granules was noted in the three layers of the adrenal cortex, most marked in the zona glomerulosa. On withdrawal of the medication, there was a reappearance of these granules. Bilateral thoracolumbar sympathectomy seemed to increase the effect produced by thiocyanate therapy.

It was concluded that a combination of a reduction in adrenal cortical function by sympathetic denervation of the adrenal medulla and depletion of the lipids of the adrenal cortex by thiocyanates would result in a more effective lowering of blood pressure than could be accomplished by either procedure alone.

ABRAMSON

Holley, H. L., Elliott, H. C., Jr., and Holland, C. M., Jr.: Serum Sodium Values in Essential Hypertension. Proc. Soc. Exper. Biol. and Med. **77:** 561 (July), 1951.

A series of serum sodium determinations were made on 75 hypertensive patients and on 400 normotensive individuals. The results obtained revealed a statistically significant rise in the serum sodium of the hypertensive patients. The authors avoided any conclusions of their results. One might be tempted to conclude that these findings support the concept of adrenal participation in the production of the hypertensive syndrome and this might offer a basis for the restriction of sodium in the treatment of hypertension. The authors believe that until the significance of these findings is more clearly understood, it may perhaps be better to avoid any definite conclusions as to their therapeutic or etiologic concepts.

MINTZ

Perera, G. A.: Altered Metabolic Response Prior to the Development of Hypertensive Vascular Disease. Am. Heart H. **42:** 308 (Aug.), 1951.

The author presents a case report of a 27 year old woman with a normal blood pressure who exhibited a pressor response to desoxycorticosterone and failed to lose weight during rigid salt restriction for 24 hours. Such responses were observed before by the author, only in hypertensive patients. Three months later, the patient developed hypertension. Since the increase in arterial tension following desoxycorticosterone and failure to lose weight under the stimulus of rigid salt restriction occurred prior to the appearance of elevation of the blood pressure, the author suggests that perhaps an altered metabolic response may exist before the development of hy-

pertension. Further search is warranted for a metabolic factor long in advance of the first signs of overt disease.

HELLERSTEIN

Hetzel, B. S.: Some Aspects of the Natural History of Hypertensive Vascular Disease. M. J. Australia **2**: 22 (Aug.), 1951.

The clinical features of a series of 203 patients with hypertension are reviewed by the authors. The known causes of hypertension accounted for only 11 per cent of the cases. "Essential" hypertension comprised 89 per cent of the cases in the series. In men, obsessional compulsive personality traits were found in 50 per cent. There was little evidence of obesity or endocrine disturbance. Family history was positive in only 19 per cent. In women, a history of toxemia of pregnancy occurred in 53 per cent of those who were parous, and in 83 per cent of these cases the hypertension dated from pregnancy. Evidence of compulsive personality traits was present in 50 per cent. A "positive" family history was present in 43 per cent.

The course of a case of hypertension is determined by the development of hypertensive vascular disease, which is characterized by diffuse arteriolar disease. "Primary" hypertension which is clinically significant appears by the age of 50 years, the blood pressure reading being at least 180 mm. Hg (systolic) and 120 mm. (diastolic).

In "primary" hypertension, the course is more rapid in men than in women. In women, the course is more rapid in those who have had an episode of toxemia of pregnancy.

The condition termed malignant hypertension is the most advanced stage of hypertensive vascular disease. It is indicated clinically by diffuse retinal edema called "papilledema", which is not produced by increased intracranial pressure but by vascular damage. This complication is especially frequent in renal hypertension and is responsible for its bad prognosis.

BERNSTEIN

Hellerstein, H. K., Orbison, J. L., Rodbard, S., Wilburne, M., and Katz, L. N.: The Effect of Rutin in Experimental Malignant Hypertension. Am. Heart J. **42**: 271 (Aug.), 1951.

The authors produced fulminating hypertension in 16 dogs by bilateral renal artery constriction. Rutin (220 mg.) prevented the characteristic hemorrhagic phenomena when administered subcutaneously 10 days before renal artery ligation and during the postoperative period. Both control and treated dogs developed equally severe uremia and the survival time was not altered. The protective action of rutin is thought to be due to its stabilizing effect on the ground substance of arterioles and of the pericapillary sheath.

HELLERSTEIN

McDowell, F. H., and Plum, F.: Arterial Hypertension Associated with Acute Anterior Poliomyelitis. New England J. Med. **245**: 241 (Aug. 16), 1951.

The authors observed 95 patients with acute or subacute poliomyelitis. Hypertension was considered present if the diastolic blood pressure was over 90 mm. Hg for more than 12 hours. Arterial hypertension developed in 45 patients. It was observed twice as frequently in males as in females. The hypertension was of greater degree and longer duration in patients needing artificial respiration. The possibility of the deleterious effect of body or tank-type respirators was considered by the authors, but hypertension was also observed in one patient treated with a rapid-rocking bed. The greatest incidence of hypertension was in those patients suffering bulbospinal paralysis or paralysis of all four extremities. Ten of the hypertensive respiratory patients still had hypertension 3 to 12 months after the onset of their acute illness. The hypertension is considered to be the result of invasion of the brain-stem autonomic structures or a manifestation of a generalized alarm reaction. Anoxemia, hypercapnia or artificial respiration seemed to intensify or prolong the otherwise transient hypertensive state.

ROSENBAUM

Handler, P., and Bernheim, F.: Effects of Caloric Restriction, Salt Restriction, and Role of Pituitary and Adrenal Glands in Experimental Renal Hypertension. Am. J. Physiol. **166**: 528 (Sept.), 1951.

A low protein diet may impair synthesis or secretion of ACTH. Rats with subtotal nephrectomies have their blood pressure returned to normal by a low protein diet and small amounts of ACTH will elevate it again. These authors investigated the influence of salt and water restriction and the role of pituitary and adrenal function in the hypertension of subtotal nephrectomy. When using circulating eosinophils as an index of ACTH secretion, the restriction of protein, salt, calories, or choline all gave indication of decreased pituitary elaboration or secretion. Since exposure to cold was still able to restore the hypertension after hypophysectomy or a low protein regime in partially nephrectomized rats, the authors suggest that neurogenic factors may be operative. Since eosinopenia was observed at the same time, the adrenal cortex is probably controlled by factors other than ACTH under these circumstances. Hyperthyroidism and dinitrophenol both elevate blood pressure in partially nephrectomized rats maintained on a low protein diet. In similar animals, cortisone effects were more marked than DCA effects. ACTH (1 mg. on two successive days, subcutaneously) produced an immediate rise in blood pressure in bilaterally nephrectomized rats to levels like those in subtotally nephrectomized rats on a normal protein intake. From these results, it is concluded that the effects of cortisone and ACTH on subtotally nephrectomized rats do not depend en-

tirely on salt retention and it is suggested that hypertension in these rats does not result from abnormal metabolism of remaining renal tissue but from failure to excrete some "pressor" material.

OPPENHEIMER

Zintel, H. A., Wolferth, C. C., Jeffers, W. A., Hafkenschiel, J. H., and Lukens, F. D. W.: Subtotal Adrenalectomy in the Treatment of Patients with Severe Essential Hypertension. Ann. Surg. **134:** 351 (Sept.), 1951.

The effect of partial removal of the adrenal gland was studied in 26 patients suffering from severe hypertension. Nine had simultaneous 95 to 98 per cent adrenalectomy, subdiaphragmatic sympathectomy and splanchnicectomy, while nine others had 88 to 98 per cent adrenalectomy as their only surgical procedure. Two patients who had evidences of severe renal damage were subjected to total removal of both adrenal glands. A two-stage operation appeared to be more satisfactory than a one-stage procedure.

The authors followed 11 patients for from 4 to 12 months postoperatively. Two of these had persistent normal blood pressure, while a third had periods of normal pressure, but the level tended to become elevated with excessive adrenal replacement therapy. Three of the patients died. All eight patients who lived showed improvement of one or more of their symptoms and were able to return to part or full time activity, whereas before adrenalectomy they had been incapacitated. Two of the patients continued to require adrenal replacement therapy.

The authors concluded that subtotal adrenalectomy will produce some beneficial effects on the signs and symptoms, as well as a variable reduction in the blood pressure, of hypertensive patients. Longer follow-up studies are necessary for the full evaluation of this procedure.

ABRAMSON

Brust, A. A., Reiser, M. F., and Ferris, E. B., Jr.: Evaluation of Neurogenic Control of Blood Pressure in Hypertension with Tetraethylammonium Chloride and Spinal Anesthesia. J. Clin. Investigation **30:** 925 (Sept.), 1951.

The authors report on comparative study of the hypotensive effects of tetraethylammonium chloride (TEAC) and spinal anesthesia (to a level of T_3 or T_6). In all subjects (11 with malignant and 13 with benign hypertension) both TEAC and spinal anesthesia significantly reduced the blood pressure. The degree of fall in blood pressure due to TEAC paralleled the effect of anesthesia. Lower blood pressure readings were obtained with TEAC, and this substance further reduced the blood pressure when administered during high spinal anesthesia. It would seem that the autonomic blockade of TEAC was more complete than that of high spinal anesthesia.

WAIFE

Zollinger, H. U.: Hypertension following Experimental X-Ray Irradiation of One Kidney in the Rat. Schweiz. Ztschr. Path. u. Bakt. **14:** 366 (fasc. 4), 1951.

In 20 adult rats, one kidney was removed and the other displaced to the subcutaneous tissue. The rats were then irradiated with 3000 roentgens per liter. Periodic blood pressure measurements taken from the tail of the 14 animals who survived the operation for 2 to 16 months, revealed two periods of hypertension. The first phase occurred in the second to third week and the second phase in the fifth week after x-ray treatment. An increase of the heart weight and histologic changes in the arterioles found at autopsy of the animals confirmed the presence of moderate hypertension. The biphasic course of the blood pressure elevation is ascribed by the authors to an early and a late effect of x-ray irradiation upon the kidney. The first peak is explained by direct damage to the tubules of the middle portion of Henle's loop, the second peak is interpreted as the result of impaired blood circulation in the secondary contracted kidney.

PICK

PATHOLOGIC PHYSIOLOGY

Seifter, S.: The Effects of Dietary Deprivation of Potassium on Heart Glycogen and on Blood Glycolysis. J. Lab. & Clin. Med. **38:** 78 (July), 1951.

Rats deprived of dietary potassium for periods of time varying from 7 to 77 days showed a comparatively rapid absolute increase in the glycogen contents of their hearts as compared with suitable controls. The cardiac glycogen level of such potassium starved rats increased to about twice the normal value, and could rapidly be restored to the control level by realimentation with potassium for several days.

Analysis of the red blood cells of the potassium starved rats for their potassium content revealed no significant deviation from the control value even after 35 days of dietary deficiency.

The rats maintained on a potassium deficient diet for 49 and 77 days respectively exhibited no significant difference from control rats in the capacity of their blood to metabolize glucose to lactic acid, and no qualitative or quantitative differences in blood glycolysis.

MINTZ

Zimmerman, H. A.: Hemodynamics: Studies on a Group of Patients Who Developed Cor Pulmonale Following Thoracoplasty. Thoracic Surg. **22:** 93 (July), 1951.

Studies were made by the author on five patients who developed cor pulmonale 8 to 15 years after thoracoplasty. These patients were encountered in the course of 650 cardiac catheterizations done under the guidance of the author. Measurements were made

of the cardiac output, oxygen consumption, blood oxygen levels, femoral artery pressure and the right ventricular pressure. All five patients had marked elevation in the pulmonary artery pressure and pulmonary resistance was markedly increased. The pulmonary diastolic pressures ranged from 100 to 500 per cent above normal. These findings are the same as those found in cor pulmonale from other causes.

It is not known why patients with thoracoplasty may develop cor pulmonale. This can occur even though the contralateral lung is free of disease.

FROBESE

Wilson, Vernon H.: Serial Femoral Arterial and Venous Blood Oxygen Studies in Anoxaemic Patients with Widespread Respiratory Disease Whilst Breathing Atmospheric Air and During Oxygen Administration. South African J. M. Sc., **16:** 15 (July), 1951.

The author demonstrated, by serial blood oxygen studies, that femoral arterial and venous blood oxygen saturations were raised during oxygen administration in patients with widespread respiratory disease and central cyanosis. The method of oxygen administration used was by nasal catheters at slow rates of oxygen flow. Twenty patients were studied. The subjects for study were chosen from patients with central cyanosis due to widespread respiratory disease in the medical and surgical wards.

Oxygen administered by nasal catheters (Tudor Edwards Spectacles—1938), at slow rates of oxygen flow, elevated the femoral arterial and venous blood oxygen saturation in the patients with widespread respiratory disease and central cyanosis, and corrected anoxemia in the majority of cases. The three patients, whose femoral arterial oxygen saturation failed to rise above eighty per cent after oxygen administration, differed from the other patients in having gross lobar absorption collapse, in addition to widespread bronchopneumonia in the rest of the lungs. Oxygen administration had a variable effect on the femoral arteriovenous blood oxygen difference. Only one of the 20 patients showed clinical evidence of oxygen want while breathing atmospheric air.

BERNSTEIN

Gilroy, J. C., and Wilson, Vernon H.: On the Relationship of Pulmonary Hypertension to Anoxaemia in Cases of Respiratory Disease with Cor Pulmonale. South African J. M. Sc. **16:** 1 (July), 1951.

The authors chose the subjects for study from patients admitted to the medical wards with widespread respiratory disease, central cyanosis and systemic venous engorgement of varying severity. At the time of the investigation, three of the patients were convalescent and, therefore, serve as a comparison to the remaining 13 patients who were still suffering from their disease during catheterization of the pulmonary arteries. It will be seen that the degree of anoxemia and the height of the pulmonary arterial pressure varied considerably in different individuals. One finding bore no real relationship to the other. The results, the authors believe, suggest that there is no constant relationship between pulmonary pressure, anoxemia and the ratio of the residual air to the total capacity of the lungs.

BERNSTEIN

Kjellberg, S. R., and Rudhe, U.: Electrokymography of the Pulmonary Artery in Cases of Pulmonary Stenosis. Acta radiol. **36:** 133 (Aug.), 1951.

The authors stress the similarity between the electrokymographic tracings in the post-stenotic portions of the aorta in coarctation and the pulmonary artery in pulmonic stenosis. The pattern, in eight cases of pulmonic stenosis, shows a slowly rising upward deflection in systole which is, at times, associated with an anacrotic notch and a partial reduction or even the complete absence of the incisura on the descending limb at the time of closure of the pulmonic valve or shortly thereafter. Of the three case reports furnished, simultaneous ventricular pressure and electrokymographic curves were obtained in one.

SCHWEDEL

Greenfield, A. D. M., Shepherd, J. T., and Whelan, R. F.: The Part Played by the Nervous System in the Response to Cold of the Circulation through the Finger Tip. Clin. Sc. **10:** 347 (Aug.), 1951.

Studies of the response to cold were made on normal subjects and on patients with sympathectomy and with peripheral nerve section. A calorimetric method was used for estimation of heat loss from the finger tip. In normal subjects the index fingers of both hands responded during the early period of exposure to cold with symmetrical vasodilatation. After blocking the ulnar nerve, cold vasodilatation was unimpaired. Cold vasodilatation occurred in the sympathectomized patients, and in the early days, after traumatic nerve section. In the cases of peripheral nerve section, tested after a sufficient time for nerve fiber degeneration to occur, only a small response was found. However the response could be increased in every case by preliminary warming. The authors agree with previously reported work that cold vasodilatation does not depend upon the integrity of the sympathetic nervous system. They reconcile conflicting views of the dependence of the response to cold upon the integrity of somatic sensory nerves by emphasizing that although cold vasodilatation is greatly reduced in the denervated finger, it is nevertheless present. While the response can take place in the absence of a local axon reflex pathway, it is much greater when the nerves are intact.

ENSELBERG

Kopelman, H., and Lee, G. de J.: The Intrathoracic Blood Volume in Mitral Stenosis and Left Ventricular Failure. Clin. Sc. **10:** 383 (Aug.), 1951.

The authors made studies before and after congestive heart failure in 11 patients with mitral stenosis and 16 with left ventricular failure. In addition, observations were made on 10 persons without heart disease. Both the direct Fick method and the dye method were used to determine cardiac output in many cases. Intrathoracic blood volume was determined by the dye method, and in some cases where the dye was injected into the pulmonary artery by a cardiac catheter, the pulmonary blood volume was calculated. Good correlation without any systematic error was found in the cardiac output determinations with the Fick method and the Hamilton dye method. The mean intrathoracic blood volume in normal subjects was 1.8 L. ± 0.28 L. (standard deviation), with a mean index of 1.14 L./sq.m. ± 0.18 L./sq.m.

A marked increase in intrathoracic blood volume was found in the cases with left ventricular failure, the mean being 2.7 L. ± 0.5, the mean index being 1.68 L./sq.m. ± 0.35. After clinical improvement the volume was only slightly decreased, being still significantly higher than normal. In mitral stenosis during failure, only a slight increase in intrathoracic blood volume was found, being 2.1 L. ± 0.42 with an index of 1.33 L./sq.m. ± 0.26. After clinical improvement the volume was very slightly above the normal values. The increase in intrathoracic blood volume could not be accounted for by changes in heart size studied roentgenologically.

The authors conclude that the main increase in intrathoracic blood volume in left ventricular failure occurs in the pulmonary vasculature, and that the persistence of increased volume after clinical improvement may be due to residual increase in pulmonary blood volume. In mitral stenosis, on the other hand, there was only a slight increase of circulating blood volume in the lungs during failure. Since in both groups, reduction in cardiac output was similar, the difference is best explained by changes in the pulmonary vasculature in mitral stenosis such as the higher pulmonary arterial pressure, anatomic changes in the pulmonary arteries and branches, active pulmonary arteriolar constriction and, in some cases, pulmonary embolic sequelae.

ENSELBERG

Lasser, R. P., and Loewe, L.: Characteristic Pressure Pulses Recorded with an Esophageal Balloon in Experimental Mitral Insufficiency in Dogs. Proc. Soc. Exper. Biol. & Med. **77:** 798 (Aug.), 1951.

Pulsations in the esophagus at the level of the left atrium were simultaneously recorded by the authors in normal dogs and in the same animals following the production of mitral insufficiency.

An identifiable and consistent pattern was observed in the esophageal tracings of normal dogs. Following the production of mitral insufficiency, characteristic alterations of the esophageal pulse wave contour were observed, which closely resembled the pressure tracings obtained simultaneously within the left atrium itself.

It was possible to detect a fall of the regurgitation pressure which resulted from hemorrhage or a rise which was produced by aortic compression. A ratio of approximately 3 to 1 was observed between the simultaneously recorded atrial and esophageal pulse pressures in the dogs with mitral insufficiency.

The authors suggest that the contour, of the pulse waves of the esophagus at the level of the left atrium, recorded with this technic, closely reflects that of the pressure pulses of the left atrium and that, within limits, a pressure relationship of a quantitative nature exists.

MINTZ

Westcott, R. N., Fowler, N. O., Scott, R. C., Hauenstein, V. D., and McGuire, J.: Anoxia and Human Pulmonary Vascular Resistance. J. Clin. Investigation **30:** 957 (Sept.), 1951.

The effect of anoxia (breathing 13 per cent oxygen in nitrogen) on the pulmonary vascular system was determined by the authors in a group of 32 patients, 21 of whom had normal cardiovascular-pulmonary systems. The others had various cardiac and pulmonary disorders. Anoxia led to an average rise of 24.6 per cent in mean pulmonary artery pressure, but there was no change in pulmonary "capillary" pressure. There was no significant alteration in cardiac output as determined by the direct Fick method. In 10 subjects, simultaneous measurements of pulmonary artery and pulmonary "capillary" pressures and cardiac output revealed that the pulmonary arteriolar resistance increased significantly (48.5 per cent) on breathing 13 per cent oxygen.

Minor changes were noted in brachial artery pressure and in total peripheral vascular resistance while the ballistocardiogram invariably became markedly abnormal during periods of anoxia.

The authors believe that the results indicate that anoxia leads to an increase in pulmonary vascular resistance through vasoconstriction, although it is not known whether this constriction is mediated through the autonomic nervous system or depends on a direct local effect.

WAIFE

VASCULAR DISEASE

Plaut, A.: Asymptomatic Focal Arteritis of the Appendix. Am. J. Path. **27:** 247 (Mar.–Apr.), 1951.

The writer has collected a series of 88 cases of necrotizing exudative arteritis of the appendix. The small arteries and arterioles in the various coats are equally involved but the tip of the appendix shows the greatest concentration of these lesions, which are barely visible to the naked eye. Microscopically,

these vessels show focal necrosis in their walls, destruction of the elastic lamellas, fibrinoid degeneration of the media, infiltration of monocytes, polymorphonuclear leukocytes and eosinophils. While necrotic material fills the lumens of many of the involved vessels, there is no thrombosis, no aneurysm formation, and no infarction.

The author stresses the fact that focal arteritis of the appendix is not related to periarteritis nodosa and that microscopic discovery of such a lesion should cause no fear of the possibility of the latter condition. It is unique in that it occurs only in the appendix. It probably plays little or no role in the development of appendicitis.

GOULEY

Duomarco, J., Rimini, R., Sapriza, J. P., and Surraco, G. H.: The Collapse of the Large Thoracic Veins. Cuore e circ. **35**: 156 (June), 1951.

Angiocardiographic studies in man show a collapse of the large veins of the chest in certain positions of the body. The large veins were visualized through injection of a radiopaque medium and evidence of collapse was given by the observation of dimmer and less regular shadows. Collapse was observed in the following conditions: (a) intrathoracic collapse of the subclavian and probably also of the jugular vein, in the upright position; (b) complete collapse of the superior vena cava, in the erect position; (c) the contrast medium did not flow from the right atrium into the inferior cava; this fact is explained with an intrathoracic collapse of the latter.

The above-described venous collapses did not occur in patients with congestive failure. In such cases, the superior cava was found distended in the upright position, and the length of the distended segment increased with the rise of venous pressure. The contrast medium flowed from the right atrium through the inferior vena cava into the hepatic veins. The intrathoracic collapse of the subclavian and jugular veins in the upright position was also found to be absent in congestive failure.

LUISADA

Hirschowitz, B. I., and Bagg, L.: Aneurysm of the Abdominal Aorta with a Report of Four Unusual Cases. Gastroenterol. **18**: 375 (July), 1951.

In 16 cases of aneurysm of the abdominal aorta presented by the authors, aneurysm of the abdominal portion of the aorta occurred in 22 per cent.

In a group of patients with thoracic aortic aneurysms, syphilis was incriminated in 31 out of 37 cases (84 per cent); but it was present in only four out of 16 (25 per cent) of the aneurysms of the abdominal portion, whereas arteriosclerosis caused 11 (69 per cent) and infected emboli 1 (6 per cent). Pain was present in the majority of the cases (66 per cent), tenderness in 75 per cent, and a mass in 63 per cent of cases. Of these masses, 80 per cent pulsated. The difficulties of accurate diagnosis were stressed, as was the value of radiography as an aid to diagnosis.

Three cases which appeared to be gastrointestinal hemorrhage were described, as well as one case in which the aneurysm eroded into the spine, transecting the cord.

BERNSTEIN

Firstbrook, J. B.: The Newer Knowledge of Atherosclerosis. Brit. M. J. 4724: 133 (July), 1951.

On the basis of present evidence, it would seem that the initiating cause of experimental atherosclerosis is the administration of cholesterol. However, because of the operation of modifying factors, not all animals receiving the same amount of cholesterol for the same length of time develop the same degree of lesions. In the first place, there is a wide variation in the degree of hypercholesteremia which develops. This variation depends probably on varying thyroid activity and possibly on other factors. In the second place, not all animals with the same degree of hypercholesteremia develop lesions at the same rate. In general, the greater the degree of hypercholesteremia the more rapid is the development of atherosclerosis. However, variations in the degree of obesity, or some factor associated with obesity, can greatly modify the response. Finally, the rate of development of lesions is influenced by the arterial blood pressure and by pre-existing damage to the arterial wall.

So far as dietary cholesterol is concerned, although the circumstantial evidence is considerable, there is no direct evidence for the hypothesis that dietary cholesterol is involved in human atherosclerosis. There is strong evidence from clinical, pathologic, and experimental studies that an eminently desirable measure in the prevention of atherosclerosis is the prevention or correction of obesity. The virtues of a low-fat diet in this connection are well known. A diet particularly low in animal fat has what may prove to be an additional virtue—a low-cholesterol content.

BERNSTEIN

Moses, M. F.: Aortic Aneurysm Associated with Arachnodactyly. Brit. M. J. 4723: 81 (July), 1951.

Two cases of arachnodactyly with aneurysmal dilatation of the ascending aorta and multiple aortic tears, without dissecting aneurysm or rupture, are reported. In cases of arachnodactyly with cardiovascular abnormality it is suggested that the aortic defects occur as often as the better-known congenital heart lesions, such as patent foramen ovale. In the adult, aortic incompetence due to dilatation of the aortic ring and ascending aorta constitute the usually associated cardiovascular anomaly. These aortic lesions, though resembling the results of acquired disease, are probably the results of progres-

sive weakening in an inherited congenital malformation of the aortic media.

BERNSTEIN

Beresford, O. D.: The Clinical Diagnosis of Dissecting Aneurysm of the Aorta. Brit. M. J. 4728: 397 (Aug.), 1951.

Dissecting aneurysm is said to be found once in every 400 to 500 necropsies, but the true incidence may be higher, as this does not include cases in which the process has healed. One in 10 cases recovers and dies from other causes. About 80 per cent of cases occur in subjects over the age of 50. In young subjects, the condition is associated with pregnancy or with a congenital narrowing of the aorta. Sixty-five per cent of cases occur in males. Hypertension is often present, but opinions differ about the exact frequency. In this series 5 of the 11 cases had evidence of hypertension. It is considered that a radial pulse is absent in only 2.8 per cent of cases and a femoral pulse in only 7 per cent, but it seems probable that peripheral vascular disturbances would be found much more often if all accessible pulses were examined at frequent intervals.

It is important to stress that often a combination of two or more syndromes will arouse suspicion of the true diagnosis. Thus, in a case presenting as coronary occlusion, the finding of diminished or absent pulsation in a peripheral vessel should call for a reconsideration of the diagnosis, as should the finding of peripheral sensory loss in a case of "perforated ulcer." Laboratory investigations are not of much assistance in diagnosis, though electrocardiography may exclude alternative cardiac diagnoses. Nor is any active treatment likely to be of use, and adequate sedation seems the most reasonable course. The average time of survival from the onset of symptoms is four to seven days. The occurrence of a quiesent stage after a dramatic onset should not dissuade the physician from giving a guarded prognosis.

BERNSTEIN

OTHER SUBJECTS

Mathis, Hazel B.: A Simple Office Procedure for Demonstrating Lupus Erythematosus Cells in Peripheral Blood. Blood **6**: 470 (May), 1951.

A simple technic for the demonstration of lupus erythematosus cells in venous blood is described. About 5 cc. of venous blood is placed in a sterile centrifuge tube containing 3 drops of liquid heparin. When sedimentation has occurred at room temperature, the supernatant plasma and the extreme uppermost level of the underlying cells are transferred to a second sterile centrifuge tube and held for 45 minutes at 37.5 C. or two hours at room temperature. The incubated plasma is then centrifuged. The sediment is smeared and stained with a Romanowsky stain. L.E. cells are more readily found at the periphery of the film and are more readily found in these films of platelet masses than in buffy coat films.

BEIZER

Lenègre, J., and Chevalier, H.: Preliminary Technical Note Concerning the Histologic Study of the Septum of the Heart. Arch. mal. coeur **44**: 512 (June), 1951.

The authors describe a new technic for microscopy of the conduction system. The whole intraventricular septum is prepared in a single block. In contrast to previously used methods, it is examined in longitudinal cuts proceeding anteriorally from its posterior part. The Tawara node and the His bundle and branches can be identified without difficulty by staining every twentieth, or even fortieth, section out of 2000 to 3000, and the whole conduction system can be studied in as few as 100 to 200 microscopic slides.

PICK

Lian, C., and Coblentz, B.: Venous Catheterization in the Course of Compression of the Superior Vena Cava. Arch. mal. coeur **44**: 634 (July), 1951.

The authors present six examples which demonstrate the diagnostic value of cardiac catheterization in the compression syndrome of the superior vena cava. In three cases, normal pressures were obtained in the right auricle and in the lower part of the vessel, a sudden pressure elevation occurred when the catheter was retracted to the level of the right clavicle, thus indicating a venous stenosis in this region. In one case, in whom occlusion of the superior vena cava was suspected on clinical grounds, the diagnosis had to be corrected to that of congestive right heart failure since pressure elevation was also found in the right auricle and ventricle. In two other subjects, failure to advance the catheter beyond the right clavicle revealed the presence of a venous occlusion in this region.

PICK

Anderson, R.: Diodrast Studies of the Vertebral and Cranial Venous Systems to Show Their Probable Role in Cerebral Metastases. J. Neurosurg. **8**: 411 (July), 1951.

In a series of 1076 verified intracranial tumors, the author found the incidence of metastatic tumors was 8.4 per cent. Since the brain is devoid of lymphatics, it is assumed that cerebral metastatic lesions are blood-borne. In such lesions as carcinoma of the lung, the route of spread to the cerebrum is along the arterial tree. However, the spread of lesions from the caval system or portal system to the brain is not easily explained. In the absence of congenital cardiac lesions this blood-borne material could not bypass the pulmonary filter. Batson postulated that the spread of carcinoma could occur by

way of the vertebral venous system. He showed that contrast media injected into the dorsal vein of the penis could pass easily along the vertebral venous system, its close association with the veins of the body wall, pelvic and shoulder girdles and lastly the venous sinuses in the cranium. This system is free of valves and the blood flow in it can be altered by postural changes and variations in intrathoracic or intra-abdominal pressures.

The authors repeated Batson's studies on 12 cadavers and obtained the same results. Then he applied similar procedures in 22 living patients with normal circulations. Here he used 20 cc. of 52.5 per cent Diodrast solution injected into the femoral or cephalic veins. By external abdominal compression, he was able to force the contrast media into the ascending lumbar veins and the vertebral venous system rather than its normal course up the vena cava. When the intrathoracic pressure was increased the contrast media injected into the cephalic vein did not go past the subclavian vein but backed up into all of the transverse cervical, scapular, deep cervical, internal jugular, external jugular and vertebral veins. When the media backed up into the cranium, the internal cerebral veins as well as the external venous sinuses were filled.

It is felt that these studies support the thesis that cerebral metastases from distant primary foci can occur via the vertebral venous system.

FROBESE

Simeone, F. A., and Felder, D. A.: The Supersensitivity of Denervated Digital Blood Vessels in Man. Surgery **30**: 218 (July), 1951.

Data on the occurrence of postdenervation supersensitivity of digital blood vessels in humans was collected. These extremities were either chronically denervated by operation or were acutely denervated by procaine block of the peripheral nerves. No attempt was made to demonstrate a difference between the effects of preganglionic and postganglionic denervation.

Observations were made of the color changes in the skin after the injection of single doses of adrenaline intravenously. It was impossible to produce the circumscribed pallor or the cyanosis of Raynaud's phenomenon unless there had been a recurrence of vasomotor activity. In the patients who had developed a recurrence of vasomotor activity, it was not necessary to inject adrenaline to produce pallor and cyanosis as they developed it when merely exposed to cold.

The authors studied five patients before and after sympathectomy with plethysmographic studies on the fifth finger. In all patients there was an increased responsiveness after sympathectomy as manifested by a greater shrinkage of the parts and a prolongation of the response subsequent to the intravenous injection of adrenaline.

The authors point out that this would conform to the demonstrable response in experimental animals. Sympathetic denervation in animals renders smooth muscle supersensitive to chemical stimulation. The chief controversy is whether or not there is a real difference between the sensitizing effects of preganglionic and postganglionic sympathectomies.

FROBESE

Steele, G. D. F.: Persistent Anxiety and Tachycardia Successfully Treated by Prefrontal Leucotomy. Brit. M. J. 4723: 84 (July), 1951.

A case is described in which persistent anxiety, tachycardia and raised basal metabolic rate unresponsive to other methods of treatment were successfully treated by bilateral prefrontal leucotomy. A year has passed without relapse. The general change in personality has been compatible with excellent social rehabilitation. The case demonstrates some problems in diagnosis and treatment.

BERNSTEIN

Fitzgerald, J. E., Webster, A., Zummo, B. P., and Williams, P. C.: Evaluation of Adequate Antepartum Care for the Cardiac Patient. J.A.M.A. **146**: 910 (July 7), 1951.

During an 11 year period, 704 mothers delivered of viable infants in the Cook County Hospital were diagnosed as having organic heart disease; 24 maternal deaths were attributed to cardiac disease and complications. This compared with 21 deaths reported from a group of only 244 women with organic heart disease who were not seen in the clinic. Of the 24 clinic patients who died, 15 had no antepartum attention whatsoever and six had inadequate care. In the entire series of 704 patients with organic heart disease, pregnancy was interrupted in only eight instances, of which three died.

The authors state that management of the pregnant woman should date back to the day of her initial illness. Marriage and pregnancy call for reevaluation of her cardiac status. During pregnancy a study should be made of the patient's functional capacity. Functional class 1 patients usually are not hospitalized until the onset of labor. Class 2 patients are admitted at the time of diagnosis and are hospitalized until they become class 1, then followed closely. Class 3 and class 4 patients are admitted for study and treatment and are hospitalized for the remainder of the gestational and puerperal periods or until compensated. The authors feel the patient with cardiac disease may be safely delivered from below if there is no obstetric contraindication. During labor the cardiac patient requires constant vigilance, and care does not end with delivery but must go through the postpartum period. The fact that only 3 of the 24 cases that died had adequate care suggests that obstetric mortality could be considerably reduced in cardiac cases by proper management.

KITCHELL

Howard, P., Leathart, G. L., Dornhorst, A. C., and Sharpey-Schafer, E. P.: The "Mess Trick" and the "Fainting Lark." Brit. M. J. 4728: 382 (Aug.), 1951.

The "mess trick" consists of suddenly compressing the chest after hyperventilation for about one minute. Hyperventilation leads to dilatation of muscle and constriction of brain blood vessels. Compression of the chest causes the victim to perform an involuntary Valsalva maneuver, which in the presence of peripheral dilatation is sufficient to reduce effective blood pressure and consequently cerebral blood flow to levels which cause unconsciousness.

The "fainting lark" consists in a subject's squatting on his haunches and hyperventilating for 20 breaths, rising rapidly to the erect posture, and immediately performing the Valsalva maneuver. Consciousness is lost within a few seconds. The mechanism is the same as in the "mess trick," with the added factor of the fall in blood pressure produced by rising from the squatting posture.

BERNSTEIN

Craddock, W. L.: Diaphragmatic Flutter with Symptoms Resembling Angina Pectoris. J.A.M.A. **146:** 1315 (Aug. 4), 1951.

The case of a transient elderly male prevaricator, whose story has been reported and published in medical journals at least six times since 1935, is again reviewed. In all reported hospitalizations there have been evidences of psychopathy, malingering, belligerency, and procacity. Aliases are numerous. The individual usually applies for hospital admission pounding the left side of the chest with his fist and complaining bitterly of "pain in my heart." Despite irregular breathing with periods of apnea, there has been no evidence of circulatory impairment or cyanosis. A loud "tick-tock" sound of unequal intensity is heard throughout the chest with the ratio of this sound to the heart beat of 3:1 or 4:1. In almost every instance the cardiac mechanism has been reported normal. On several occasions the patient has had transient hyperthermia with temperature elevations of 109 to 112 F., checked by rectum, mouth, and axilla. This, plus the bizarre behavior of the diaphragm, remains unexplained in his case.

KITCHELL

Gilley, E. W., McCord, M. C., and Taguchi, J. T.: Acute Nonspecific Pericarditis. Am. J. M. Sc. **222:** 249 (Sept.), 1951.

The importance of differentiating acute benign pericarditis from myocardial infarction is emphasized in this clinical study of nine patients in whom the diagnosis of pericarditis was established. Among the clinical features discussed as being helpful in the differential diagnosis of these two conditions are the following items: (1) an antecedent respiratory infection is frequently observed in pericarditis; (2) chest pain in pericarditis resembles that of myocardial infarction except that it is often distinctly accentuated by respiration; (3) the pericardial friction rub of pericarditis occurs early, is of greater intensity and more widespread than that of infarction; (4) fever, leukocytosis and increased sedimentation rate occur earlier in pericarditis than in myocardial infarction; (5) chest x-rays may show cardiac enlargement with rapid changes noted in heart size in pericarditis, and pulmonary abnormalities are those of pleuritis or pneumonitis; in myocardial infarction, the heart size does not show rapid changes and the pulmonary abnormalities noted are usually those of congestion; (6) the electrocardiogram in pericarditis shows serial changes of S-T segment elevations without reciprocal T-wave inversion until later when the S-T segment is isoelectric; QRS patterns are not abnormal in pericarditis.

In 2 patients paroxymal supraventricular tachycardia was observed during their illness. One patient, treated with heparin and dicoumarin for supposed myocardial infarction, died on the twelfth day of therapy as a result of cardiac tamponade produced by hemorrhage into the pericardial sac.

SHUMAN

BOOK REVIEWS

Traité des maladies des veines. *Charles Laubry and Jacques Louvel.* Paris, G. Doin, 1950. 376 pages, 53 figures. Price 1,700 fr.

This book attempts to organize briefly all our present knowledge of the diseases of veins. Toward that end, the anatomy, histology, and physiology are dealt with briefly, as well as the methods and technics for clinical examination, and the pathology of venous thrombosis. In the clinical presentation, the author discusses phlebothrombosis and phlebitis, with a special chapter on venous insufficiency. The subjects of phlebosclerosis and other diseases are dealt with briefly. The authors finally discuss at some length the appropriate therapeutic and prophylactic measures to be adopted.

In general, this is a valuable addition to the relatively scant number of monographs and books on veins. This is one of the very few books which have tried to cover both the basic knowledge and the clinical and therapeutic aspects of venous diseases. It will prove especially useful to the clinician, surgeon and medical student, who will find here a succinct and all inclusive introductory discussion of venous diseases. It will, however, disappoint the histologist and pathologist since the discussion of the histology and pathology is inadequate, and the histologic illustrations are of poor quality. Likewise, the discussion of phlebosclerosis is too brief to be informative.

These comments should not detract from the fact that the authors have dealt with a subject which has been badly neglected by others. This book is a useful addition to the clinician and surgeon.

MAURICE LEV

Electron Microscopic Histology of the Heart. An Application of Electron Microscopic Research to Physiology. *Bruno Kisch, in collaboration with Joan M. Bardet.* New York, Brooklyn Medical Press, 1951. 106 pages, 62 figures. $5.00.

The author's great enthusiasm for the study of heart muscle by electron microscopy, which permits the visualization of ultramicroscopic structures, is obvious throughout the book, and his views are epitomized in the statement that this method will prove to be "the indispensable tool for all future cardiology, including pharmacology and clinic (sic) of the heart." Many features observable by electron microscopy, not detectable by light microscopy, led the author to believe that the details revealed by the method may prove to be "of great importance for the better understanding of the biochemistry of heart muscle under normal conditions, in coronary insufficiency, in circulatory failure, in anemia and in other conditions of clinical importance." He insists that the information about the biochemistry, physiology, and other normal features of heart muscle which derives from electron microscopic histology, involving a study of the relationships between the organelles of whole myocardial fibers, is far superior to that which can be obtained by electron microscopy of particles. He visualizes great improvement in the method of electron microscopic histology from the development of specific staining methods of tissues, for this special purpose, and predicts great advances in our knowledge from electron histology of heart muscle before and after the administration of drugs which affect the heart. He is fully aware of the existing drawbacks of the way in which such studies must be carried out at present and realizes that such conditions as high temperatures, vacuum and electron bombardment may introduce artefacts, which certainly means that this type of examination cannot be applied to living tissues.

In his studies, the first to be made on the heart by this method, the author compares the similarities and differences of the electron microscopic appearance of heart muscle with the same tissue examined by light microscopy. He found that in each cardiac muscle fiber there are from 300 to 700 myofibrils, the most primitive contractile units of the heart. A reticulated system of Z bands connected with the sarcolemma keeps the myofibrils in place. Capillaries actually enter the muscle fibers, to supply sarcoplasm, nuclei and myofibrils with blood, confirming the opinion that the nearly inexhaustible working capacity of the heart muscle depends to a great extent on the large amount of intra- as well as extrafiber capillaries as well as on the tremendous wealth of enzyme-bearing sarcosomes, some of which are scattered between the myofibrils, while others are massed at the poles of the nuclei, but which are never present inside the myofibrils. These and many other details of the minute structures of heart muscle are given in the book.

The author attempts to interpret the physiologic action of every identifiable structure but admits that the part played by some of the structures is still open to question. The inadequacy of the photo-

graphs of tissue sections, by the method of electron microscopy, as compared with the remarkable results obtained with the aid of metal shadowing, which can be carried out on particles, is admitted by the author, but it is his belief that the goal he has in mind "cannot be reached by the most wonderful pictures of fractions of tissue elements."

HARRY GOLDBLATT

Tobacco and the Cardiovascular System. The Effects of Smoking and of Nicotine on Normal Persons. *Grace M. Roth.* Springfield, Ill., Charles C. Thomas, 1951. 66 pages, 1 table, 8 figures. $2.25. (American Lecture Series in Circulation No. 100.)

The effects of the use of tobacco have too long been debated on sentimental grounds and too often the advice of the physician has been colored by his own habits or bias. Fortunately, during the past 25 years, it has been possible to measure the effects of smoking on certain segments of the cardiovascular system and from data thus obtained significant conclusions may be drawn. There are aspects of the problem which require further study. Dr. Roth has pursued this subject diligently and productively in the clinic and the laboratory. This modest monograph summarizes the present knowledge with objective precision. In it Dr. Roth has condensed years of experimental studies and has evaluated the available clinical evidence. The marked vasoconstricting effects of tobacco have been conclusively documented. She has presented sound evidence that the drinking of alcohol will not protect the individual against the vasoconstricting effects of tobacco and has answered many other questions of theory and practice. This book is recommended reading for all physicians and many of their patients.

IRVING S. WRIGHT

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ASSOCIATION FELLOWSHIPS

Applications for Established Investigators and for Research Fellows must be received not later than September 15, 1952. Information and forms may be obtained from the Medical Director.

ANNUAL ELECTIONS

Officers

Dr. Irving S. Wright, New York, assumed the Presidency of the Association for the 1952–53 term at the Twenty-Eighth Annual Meeting in Cleveland in April. Dr. Wright is Professor of Clinical Medicine, Cornell University Medical College, and attending physician at New York Hospital. He is a Past President and board member of the New York Heart Association, and has served as Chairman of the national Association's Committee on Anticoagulants and Publications Committee. Dr. Wright succeeds Dr. Louis N. Katz, Chicago, who succeeded to the Chairmanship of the Scientific Council.

Dr. Robert L. King, Seattle, was chosen President-Elect. Dr. King is a partner in the Mason Clinic, Seattle, a Past President of the Washington State Heart Association, and a former Vice-President of the national Association.

Re-elected as Vice-Presidents were Mrs. Alben W. Barkley, Washington; Bruce Barton, New York; T. Duckett Jones, M.D., New York; and Frederick K. Trask, Jr., New York. Vice-Presidents elected to serve for the firs

ime included Edgar V. Allen, M.D., Rochester, Minn.; E. Cowles Andrus, M.D., Baltimore; Irvine H. Page, M.D., Cleveland; and John J. Sampson, M.D., San Francisco. Berkeley D. Johnson, New York, was elected Treasurer.

Board of Directors

New members of the Board of Directors, elected by the Assembly for a three-year term are: Ben May, Mobile, Ala.; Hugh Morgan, M.D., Nashville, Tenn.; and John Talbott, M.D., Buffalo, N. Y.

Re-elected to the Board for three-year terms were John D. Brundage, Newark, N. J.; Mrs. Douglass O. Burnham, Watertown, Conn.; W. Montague Cobb, M.D., Washington; George K. Fenn, M.D., Chicago; A. J. Hayes, Washington; John C. Higgins, Vancouver, Wash.; David J. McDonald, Pittsburgh; Frank L. Mechem, Seattle; Michel E. Puyans, New York; Howard B. Sprague, M.D., Boston; C. J. Van Slyke, M.D., Bethesda, Md.; and J. Ross Veal, M.D., Washington.

New members elected to the Board for a two year term include Edgar Hull, M.D., New Orleans; Paul V. Ledbetter, M.D., Houston; Louis E. Martin, M.D., Los Angeles; S. E. McCreless, San Antonio; and David S. Robertson, Los Angeles.

Newly elected Board members for one year are Edwin P. Maynard, Jr., M.D., Brooklyn, N. Y.; E. Sterling Nichol, M.D., Miami; and Eugene Stead, M.D., Durham, N. C.

Board members chosen to represent the Scientific Council and its component sections and councils include: Nelson Barker, M.D., Rochester, Minn.; Francis L. Chamberlain, M.D., San Francisco; Charles A. R. Connor, M.D., New York; Arthur C. DeGraff, M.D., New York; Thomas M. Durant, M.D., Philadelphia; John P. Hubbard, M.D., Philadelphia; Frank E. Joseph, Cleveland; Adrian D. Joyce, Cleveland; Louis N. Katz, M.D., Chicago; Chester M. Kurtz, M.D., Madison, Wis.; R. Bruce Logue, M.D., Atlanta; and Hugh Montgomery, M.D., Philadelphia.

GOLD HEART AWARDS

Gold Heart Awards for outstanding contributions to cardiovascular medicine or the Association were presented at the Annual Dinner in Cleveland in April to A. W. Robertson, Dr. Carl J. Wiggers, the late Robert L. Mehornay, and Mrs. Albert D. Lasker. Mr. Robertson, chairman of the Finance Committee and member of the Board of Directors of Westinghouse Electric Corporation, was honored for his leadership as Board Chairman of the Association from 1948–52. Dr. Wiggers, who is Professor and Director of the Department of Physiology at Western Reserve School of Medicine, received this award in recognition of his influence on medical thinking and for his unique training school for research investigators. Last year Dr. Wiggers was honored for his work in the field of cardiovascular physiology by dedication of a special issue of CIRCULATION. The posthumous award to Mr. Mehornay, business and civic leader of Kansas City, Mo., was presented in recognition of Mr. Mehornay's contributions to the development of the Association as one of the first lay members of the Board of Directors. Mrs. Lasker, co-founder of the Albert and Mary Lasker Foundation, received the Gold Heart for the contributions she has made in focusing public, professional and governmental attention on the need for medical research on heart and other diseases which are the main killers and cripplers.

NEW MEDICAL DIRECTOR

Dr. Charles D. Marple, Assistant Clinical Professor of Medicine at the University of California School of Medicine since 1950, has been appointed Medical Director of the Association.

In his new position, Dr. Marple will administer the research policies and scientific program, as developed by the Association's Scientific Council, and will also be responsible for conducting the program of physician education.

As a Research Fellow of the American Heart Association, Dr. Marple served as coordinator of the Committee on Anticoagulants at the New York Hospital from 1947–49. While at the University of California, he was engaged in a survey for the coordination of cardiovascular research.

A native of California, Dr. Marple received his M.D. at Stanford University in 1938. He served a year's rotating internship at San Fran-

cisco City and County Hospital, followed by a year as resident physician, rotating service, at Tulare County General Hospital, Tulare, Cal. He spent an additional year as assistant resident physician at Stanford University School of Medicine and Stanford Hospital, before entering private practice.

In addition to his practice, he was Assistant Chief Surgeon, California State Prison from 1940 to 1942. Dr. Marple served in the Army Medical Corps during World War II, and became chief of the Communicable Disease Section at the Santa Ana Army Air Base, Santa Ana, Cal., in 1946. He subsequently became resident physician in internal medicine at Los Angeles County General Hospital. From 1943 to 1949, Dr. Marple was Associate Editor of "Clinical Medicine."

REVISED CLASSIFICATION CHART

The Association has issued a revision of the chart, "Classification of Patients with Diseases of the Heart," which has gained wide acceptance as a guide to functional capacity and therapeutic classification of cardiac patients.

The chart, which has been adopted by the Association, was revised by the Criteria Committee of the New York Heart Association. This Committee is preparing, under the chairmanship of Dr. Harold E. B. Pardee, the fifth edition of the book, "Nomenclature and Criteria for Diagnosis of Diseases of the Heart," which will include the revised chart. The chart is being distributed by state and local heart association affiliates to physicians, hospitals, vocational counselors, social workers and others concerned with the cardiac patient.

ANNUAL REPORT

The Association's 1951 Annual Report has been published, and copies are available upon request.

GRANTS FOR COLOR ILLUSTRATIONS

For the year 1952, the American Heart Association has received a grant of $3,000 from Winthrop-Stearns, Inc., to be used for colored illustrations in CIRCULATION. Grants for the same purpose were given by Wyeth, Inc., for the two preceding years.

Since color is essential in properly illustrating certain scientific matters, the Association is most grateful for these generous gifts.